CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206619Orig1s000

CHEMISTRY REVIEW(S)

ADDENDUM

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

DATE: December 18, 2014
FROM: Caroline Strasinger, Ph.D., Review Chemist, Branch V/ONDQA
THROUGH: Rapti Madurawe, Ph.D., Branch Chief, Branch V/ONDQA
TO: CMC Review #2 for NDA 206619
SUBJECT: Addendum

The previous CMC Review #2, dated 11-NOV-14, made a recommendation of not approvable due to a pending recommendation from the Office of Compliance.

The Office of Compliance has made a recommendation of **Approvable** on 18-DEC-2014. Refer to the manufacturing recommendation below.

Conclusion and Recommendation: From the ONDQA perspective, this NDA is recommended for APPROVAL.

(b) (4)

NDA 206619

Viekira Pak
(ombitasvir, paritaprevir and ritonavir tablets copackaged with dasabuvir tablets)

AbbVie Inc.

Maotang Zhou, Ph.D. – Drug Substance
Milton Sloan, Ph.D. – Drug Substance
Caroline Strasinger, Ph.D. – Drug Product

Review Chemists

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

Addendum #1 to CMC Review #1 of NDA 206619

For the Division of Antiviral Products

Chemistry Review Data Sheet

1. NDA 206619

2. REVIEW #: #2

3. REVIEW DATE: 14-NOV-2014

4. REVIEW TEAM: Caroline Strasinger, Ph.D.
Maotang Zhou, Ph.D.
Milton Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	19-SEP-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document Date
Amendment 0037	25-SEP-2014
Amendment 0038	30-SEP-2014
Amendment 0044	17-OCT-2014
Amendment 0045	22-OCT-2014
Amendment 0049	30-OCT-2014
Amendment 0051	06-NOV-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	AbbVie, Inc
Address:	1 N. Waukegan Road Department PA77 Bldg. AP 30 North Chicago, IL 60064
Representative:	Troy ZumBrunnen, Pharm D, Director, Regulatory Affairs
Telephone:	847-938-9445

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Viekira Pak
b) Non-Proprietary Name (USAN): ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets
c) Code Name/#:
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: treatment of chronic hepatitis C virus GT1 infection in adults, including those with compensated cirrhosis, who are either treatment-naïve or previously treated with pegylated interferon (pegIFN) and ribavirin

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 12.5 mg/75mg/50 mg (ombitasvir/paritaprevir/ritonavir tablets) and 250 mg (dasabuvir tablets)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

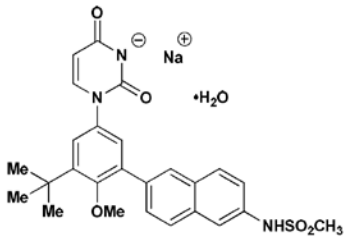
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

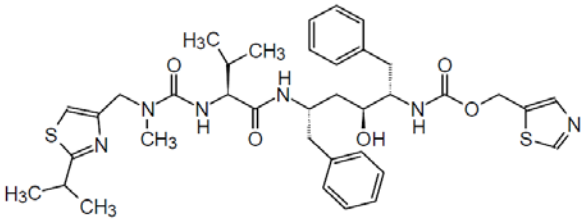
Dasabuvir Sodium:

Figure 1. Structure of Dasabuvir Sodium



Molecular Formula:	$C_{26}H_{26}N_3O_5S•Na•H_2O$ (salt, hydrate); $C_{26}H_{27}N_3O_5S$ (free acid, anhydrate)
Molecular Weight	533.57 (salt, hydrate); 493.57 (free acid, anhydrate)

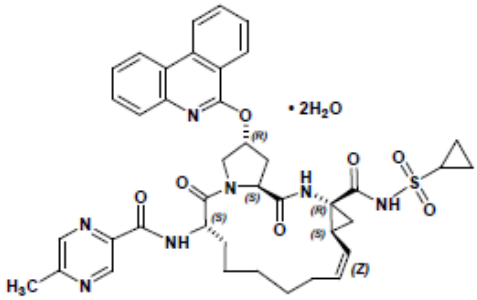
Ritonavir:



RITONAVIR

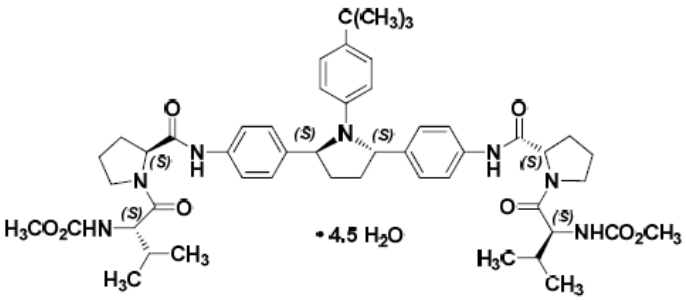
Molecular Formula: $C_{37}H_{48}N_6O_5S_2$
Molecular Weight: 720.95

Paritaprevir:



Molecular Formula:	$C_{40}H_{43}N_7O_7S•2H_2O$ (dihydrate); $C_{40}H_{43}N_7O_7S$ (anhydrous)
Molecular Weight:	801.91 (dihydrate); 765.88 (anhydrous)

Ombitasvir:



Molecular Formula:	$C_{50}H_{67}N_7O_8 \cdot 4.5\ H_2O$ (hydrate) $C_{50}H_{67}N_7O_8$ (anhydrate)
Molecular Weight	975.20 (hydrate); 894.11 (anhydrate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20659	Ritonavir Oral Solution
NDA	22417	Ritonavir Tablets
IND	103526	ABT-450
IND	108434	ombitasvir

IND	101636	dasabuvir

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	PENDING	8-AUG-14	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Acceptable	21-SEPT-14	Elsbeth Chikhale
LNC	N/A		
Methods Validation	Pending	8-AUG-14	
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	5-AUG-14	Caroline Strasinger
Microbiology	Adequate	6-MAY-14	Erika Pfeiler

ADDENDUM #1 to the Chemistry Review #1 for NDA 206619

THE EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

Labels and labeling (Description and How Supplied sections) have been finalized from a CMC perspective

An overall "Acceptable" recommendation has ***not*** been made by the Office of Compliance as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form at this time. The NDA can be recommended for approval once an acceptable recommendation has been made by the Office of Compliance.

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

A Post Marketing Commitment (PMC) related to product quality has been agreed upon by the Applicant and FDA on 06-NOV-2014 regarding continued development for a test for (b) (4) with a sensitivity of (b) (4)% in the ombitasvir, paritaprevir, ritonavir drug product tablet for the release and stability specification.

Proposed final report submission: December 31, 2016.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product:
AbbVie's NDA 206619 provides for VIEKIRA PAK (ombitasvir, paritaprevir and ritonavir tablets copackaged with dasabuvir tablets), an immediate-release solid oral dosage therapy for the treatment of chronic HCV GTI infection in adults. VIEKIRA PAK consists of 2 pink, film-coated

ombitasvir/paritaprevir/ritonavir fixed dose combination (FDC) tablets copackaged with 2 beige, film-coated dasabuvir tablets in an aluminum blister. Each FDC tablet has AV1 printed on one side and contains 12.5mg/75mg/50mg of ombitasvir/paritaprevir/ritonavir drug substance respectively. Each dasabuvir tablet has AV2 printed on one side and contains 270.26 mg of dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir base. Ombitasvir, paritaprevir and dasabuvir are all New Molecular Entities (NME).

Ombitasvir, paritaprevir and ritonavir drug substance are each formulated (b) (4) at **AbbVie** (b) (4) before being further processed into the final FDC tablets at **AbbVie Inc.** in **North Chicago, IL**. The ritonavir (b) (4) is referenced to AbbVie's NDA 22417 for Ritonavir Tablets (b) (4)
The dasabuvir tablet is manufactured at **AbbVie Ireland** in **Sligo, Ireland**. Several additional domestic and international sites have been listed as excipient testing and packaging facilities for Viekira Pak.

The quality of the drug products are controlled by tests for description, identity, assay, (b) (4) content uniformity, degradation products, and dissolution. (b) (4) A test for (b) (4) has been added to the specification for the combined tablet since review #1. All final specifications are given in Appendix 3 of this addendum. A comprehensive risk assessment of each tablet is given in section C of the Executive Summary.

The commercial container closure system is a push through aluminum blister pack within a cardboard wallet and then packaged as a seven day supply in a cardboard carton. Viekira Pak is granted an expiration dating of 24 months when stored at or below 30ºC (86ºF). The expiration dating is supported by 18 months of long-term registration stability data for the dasabuvir and FDC tablet, and multiple supportive data (such as site specific, stability challenging, (b) (4) stability, and stability data from tablets manufactured (b) (4)). (b) (4)

Drug Substances:
Dasabuvir
Dasabuvir is a new molecular entity. The drug substance, dasabuvir sodium, is a white to pale yellow to pink powder. The drug substance is manufactured as monosodium salt monohydrate (b) (4) Dasabuvir sodium is not hygroscopic and has low solubility by BCS criteria. Dasabuvir has no chiral centers and is optically inactive. (b) (4)

The dasabuvir sodium drug substance is manufactured [redacted] The specifications for dasabuvir sodium drug substance includes tests for description, identification, assay, impurities, sodium content, residual solvents, [redacted] water content, residual heavy metals, and microbiological quality. As revised, the acceptance criteria for the tests are acceptable to ensure identity and quality of the drug substance. The proposed commercial scale batch is about [redacted] kg. Satisfactory batch analysis data from 20 batches of the drug substance manufactured on scales ranged from [redacted] Kg are provided. Up to 24 months long term and 6 months accelerated stability data are provided, along with up to 48 months data from supportive batches. Based on the data, dasabuvir sodium drug substance is granted a retest period of [redacted] months when stored at [redacted] °C.

Ritonavir

Ritonavir is used as a pharmacokinetic enhancer in Ombitasvir/Veruprevir/Ritonavir Film-Coated Tablets. AbbVie incorporates ritonavir drug substance CMC information into this NDA as agreed by FDA by cross-reference to previously submitted information in AbbVie's Norvir Oral Solution NDA (20-659). As requested by FDA, AbbVie includes a single drug substance element in Module 3 to clarify that all drug substance information is cross-referenced to the Norvir NDA. No substantial review on Ritonavir drug substance is carried out during this review cycle.

Paritaprevir

Paritaprevir drug substance is white to off-white powder with very low water solubility. Paritaprevir is manufactured [redacted] as a dihydrate. [redacted] Paritaprevir is manufactured [redacted] The majority of the drug substance manufacturing process control strategy elements is traditiona [redacted] The control strategy used ensures process

performance and drug substance quality. [redacted]

Paritaprevir drug substance has low aqueous solubility and moderate permeability. These drug substance characteristics require a [redacted] formulation. The final drug product delivers paritaprevir [redacted] using a [redacted] manufacturing process.

The drug substance specifications include tests for description, identification, [redacted] assay, impurities, genotoxic impurities, residue on ignition, water and microbiological attributes. Eighteen months of long-term and 6 months accelerated stability data were provided at the time of NDA submission along with supportive stability data. Based on the data, paritaprevir is granted a retest period of [redacted] months when stored below [redacted] °C.

Ombitasvir

Ombitasvir drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. It is manufactured [redacted] as a 4.5 hydrate. [redacted] Ombitasvir drug substance is manufactured [redacted] The manufacture of ombitasvir uses a traditional control strategy. [redacted]

Ombitasvir has very low aqueous solubility of 0.01 to 0.5 µg/mL over the physiological pH range. [redacted]

The drug substance specifications include tests for description, identification, [redacted], assay, impurities, genotoxic impurities, carcinogenic impurities, residue on ignition, water and microbiological attributes. Twenty four months of long-term and 6 months accelerated stability data were provided at the time of NDA submission along with supportive stability data. Based on the data, ombitasvir drug substance is granted a retest period of [redacted] months when stored below [redacted] °C.

B. Description of How the Drug Product is Intended to be Used

VIEKIRA PAK (ombitasvir, paritaprevir and ritonavir tablets copackaged with dasabuvir tablets), 12.5mg/75mg/50mg and 250mg, is an orally administered tablet therapy for the treatment of chronic HCV GTI infection in adults. Each VIEKERA PAK contains a one-day dose of two ombitasvir/paritaprevir/ritonavir tablets and two dasabuvir tablets. Two pink ombitasvir/paritaprevir/ritonavir tablets and one beige dasabuvir tablet are taken in the morning (A.M.) followed by one beige dasabuvir tablet taken in the evening (P.M.). All tablets are to be taken orally with food. The daily tablet combination is packaged in a blister pack in a wallet configuration design with instructions for daily use. Seven wallet VIEKIRA PAKs are then packaged in a secondary carton for weekly use. The product should be stored at or below 30ºC (86ºF).

C. RISK ASSESSMENT

Dasabuvir Tablet

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	(b) (4)				
Physical stability (solid state)					
Content uniformity					
Microbial limits					
Dissolution – BCS Class II & IV					

Impurities	(b) (4)
Particle size of drug substance	
(b) (4)	

Ombitasvir, Paritaprevir and Ritonavir Tablet

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Stability	(b) (4)				
Physical stability (b) (4)					
Content uniformity					

Microbial limits	(b) (4)
Dissolution – BCS Low Solubility	
Impurities	
(b) (4)	
Particle Size of Drug Substance	

D. Basis for Not-Approvability Recommendation

Sufficient information has been provided in the NDA to assure the quality of the drug substances and the drug product. However, the NDA is not recommended for approval at this time due to the following,

- **The Office of Compliance has not yet made an Overall Acceptable site recommendation**

The NDA can be recommended for approval upon resolution of the pending issue.

Reviewer Notes:

The previous CMC Review #1, dated 19-SEP-14, made a recommendation of not approvable due to several pending items including the following:

1. An overall "Acceptable" recommendation has ***not*** been made by the Office of Compliance.
2. All labels and labeling (Description and How Supplied sections) had not been finalized.
3. The Biopharmaceutics review was pending.
4. A CMC information request was outstanding.

These pending items are addressed in this addendum to review #1.

Additional Information was provided to the NDA and to the Review Team after Quality Review #1 dated 19-SEP-2014 was filed. This information is also reviewed below and did not result in an extension of the review clock.

Regarding Item #1, The overall site recommendation is still pending. Please see Appendix 1 for the EES report.

Regarding Item #2, CMC comments and recommendations regarding the labels/labeling were communicated to the Applicant during labeling negotiations.

Note: AbbVie's preferred storage statement, "Store at or below 30ºC (86ºF)," is slightly different from CMC's current general recommendation for a product that is stable at the world-wide long term stability condition of 30ºC/75%RH of "Store below 30ºC (86ºF)." However, because FDA does not have any official policy on exactly how to state this type of storage recommendation, based on AbbVie's provided reasoning (email dated 9-OCT-2014) for the preference CMC finds AbbVie presentation acceptable.

Excerpt from email dated 9-OCT-2014 regarding storage statement:

From: ZumBrunnen, Troy L [mailto:troy.zumbrunnen@abbvie.com]
Sent: Thursday, October 09, 2014 3:22 PM
To: Schumann, Katherine
Cc: Rogers, Sarah R
Subject: RE: NDA 206619 - Comment regarding carton and container labels

Katie,

Please find below two counter proposals regarding the salt statement and storage conditions.

1. AbbVie would prefer to specify that the product contains the monohydrate salt. The proposal to include 'mono' prior to hydrate is below.

   Each tablet contains 270.3 mg dasabuvir sodium **mono**hydrate equivalent to 250 mg dasabuvir

   Is the addition of modifier 'mono' prior to hydrate acceptable?

2. Regarding removal of the '"at or" statement in the storage conditions, AbbVie is concerned that the instructional statement "Store below 30°C (86°F)" would increase patient confusion should the product be stored at 30°C (86°F), or exposed to that

temperature for a period of time. The inclusion of the "*at or*" in the statement would assure a patient and/or customer that storage at 30°C (86°F)is acceptable and avoid potential interruption in therapy due to their uncertainty of the quality of the product. While the frequency of this occurring (a patient storing the product at exactly 30°C) may be low, we believe it is worth retaining the clarity in the label.

Is it acceptable to retain the statement on storage conditions as " Store at or below 30°C (86°F)"?

Regards, Troy

The Applicant accepted all other CMC associated changes to the label and labeling.

Reviewer Evaluation: All the labels and labeling are now adequate (see the Appendix 2).

Regarding the Item #3, the Biopharmaceutics Review was completed and recommended approval of the NDA on 21-SEP-2014. No pending issues associated with the dissolution method or other biopharmaceutics review items remain.

Reviewer Evaluation: The Biopharmaceutics review is now filed in DARRTS and recommends approval of the NDA.

Regarding the Item #4
On 17-SEP-2014 an IR was sent identifying seven areas of concern. Through a series of amendments to the NDA, the seven items were addressed and **the outstanding CMC IR cited in Quality Review #1 is now adequate.** The IR items are reviewed below in detail.

17-SEP-2014 CMC IR (NDA Amendment 09/25/14, NDA Amendment 09/30/14, NDA Amendment 10/17/14)
CMC Question #1
Establish a test and acceptance criterion for the detection (b) (4) of each drug substance in the Ombitasvir/Paritaprevir/Ritonavir Drug Product Release and Stability Specification. The method should be sensitive enough to detect (b) (4) for each of the drug substances.

Applicant Response: The Applicant agreed to add a test for detection of (b) (4) for each of the three drug substances to the triple tablet and will be based on (b) (4) methods detailed in the NDA and utilized during development studies. The Applicant updated the specification table and the impacted Module 3 documents on 17-OCT-2014. AbbVie provided the following additional information regarding the detectability of drug substance (b) (4) on 25-SEP-2014.

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/s/

ALTHEA CUFF
11/14/2014

NDA 206619

Viekira Pak
(ombitasvir, paritaprevir and ritonavir tablets copackaged with dasabuvir tablets)

AbbVie Inc.

Maotang Zhou, Ph.D. – Drug Substance
Milton Sloan, Ph.D. – Drug Substance
Caroline Strasinger, Ph.D. – Drug Product

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V

CMC Review of NDA 206619
For the Division of Antiviral Products

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Chemistry Review Data Sheet

1. NDA 206619

2. REVIEW #: #1

3. REVIEW DATE: 19-SEP-2014

4. REVIEWERS:

Primary:

Reviewer	NDA CTD Section
Milton Sloan, Ph.D.	Drug Substance: Ombitasvir Drug Substance: Paritaprevir
Maotang Zhou, Ph.D.	Drug Substance: Dasabuvir sodium Drug Substance: Ritonavir
Caroline Strasinger, Ph.D.	Drug Product

Secondary:

Reviewer	Section
Rapti Madurawe, Ph.D.	Drug Substance: Ombitasvir Drug Substance: Paritaprevir
	Drug Substance: Dasabuvir sodium Drug Substance: Ritonavir Drug Product

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Chemistry Review Data Sheet

Submission(s) Reviewed	Document Date
Original	21-APR-2014
Amendment 0018	14-JUL-2014
Amendment 0019	18-JUL-2014
General Correspondence	24-JUL-2014
Amendment 0022	25-JUL-2014
Amendment 0031	25-AUG-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	AbbVie, Inc
Address:	1 N. Waukegan Road Department PA77 Bldg. AP 30 North Chicago, IL 60064
Representative:	Troy ZumBrunnen, Pharm D, Director, Regulatory Affairs
Telephone:	847-938-9445

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Viekira Pak
b) Non-Proprietary Name (USAN): ombitasvir, paritaprevir, ritonavir tablets copackaged with dasabuvir tablets
c) Code Name/#:
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: treatment of chronic hepatitis C virus GT1 infection in adults, including those with compensated cirrhosis, who are either treatment-naïve or previously treated with pegylated interferon (pegIFN) and ribavirin

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 12.5 mg/75mg/50 mg (ombitasvir/paritaprevir/ritonavir

tablets) and 250 mg (dasabuvir tablets)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

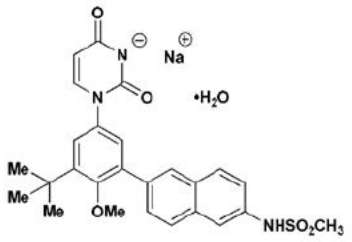
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

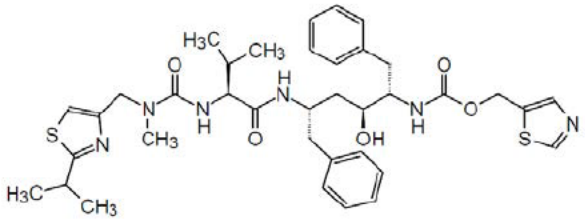
Dasabuvir Sodium:

Figure 1. Structure of Dasabuvir Sodium



Molecular Formula:	$C_{26}H_{26}N_3O_5S•Na•H_2O$ (salt, hydrate); $C_{26}H_{27}N_3O_5S$ (free acid, anhydrate)
Molecular Weight	533.57 (salt, hydrate); 493.57 (free acid, anhydrate)

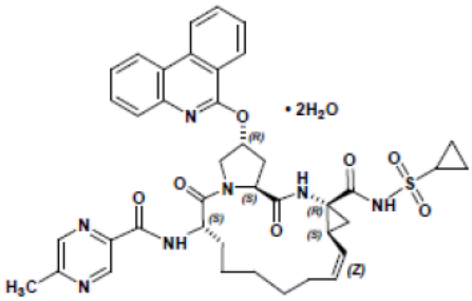
Ritonavir:



RITONAVIR

Molecular Formula: $C_{37}H_{48}N_6O_5S_2$
Molecular Weight: 720.95

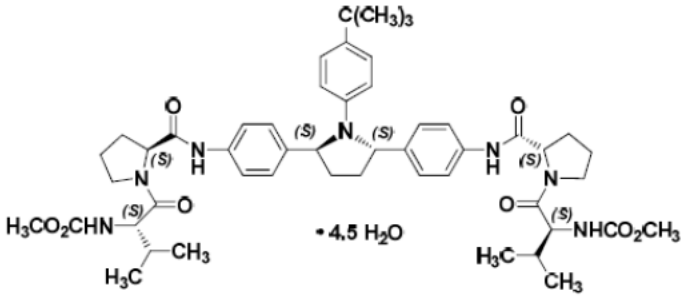
Paritaprevir:



Molecular Formula: $C_{40}H_{43}N_7O_7S \cdot 2H_2O$ (dihydrate); $C_{40}H_{43}N_7O_7S$ (anhydrous)

Molecular Weight: 801.91 (dihydrate); 765.88 (anhydrous)

Ombitasvir:



Molecular Formula: $C_{50}H_{67}N_7O_8 \cdot 4.5\ H_2O$ (hydrate) $C_{50}H_{67}N_7O_8$ (anhydrate)

Molecular Weight 975.20 (hydrate); 894.11 (anhydrate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20659	Ritonavir Oral Solution
NDA	22417	Ritonavir Tablets
IND	103526	ABT-450
IND	108434	ombitasvir
IND	101636	dasabuvir

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	PENDING	19-SEP-14	Office of Compliance
Pharm/Tox	N/A		
Biopharm	PENDING	19-SEP-14	Elsbeth Chikhale
LNC	N/A		
Methods Validation	PENDING	19-SEP-14	Division of Pharmaceutical Analysis
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	5-AUG-14	Caroline Strasinger
Microbiology	Adequate	6-MAY-14	Erika Pfeiler

The Chemistry Review for NDA 206619

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Although this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product, the Biopharmaceutics review is pending at this time, and a CMC information request is outstanding as of the date of this review.

An overall "Acceptable" recommendation has ***not*** been made by the Office of Compliance.

Labels and labeling (Description and How Supplied sections) will be finalized during labeling team review. Revisions to the CMC sections of the labeling are marked up in this review.

Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form at this time. Upon resolution of the pending issues, the NDA can be recommended for approval.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product:
VIEKIRA PAK (ombitasvir, paritaprevir and ritonavir tablets copackaged with dasabuvir tablets) is an immediate-release solid oral dosage therapy. VIEKIRA PAK consists of 2 pink, film coated ombitasvir/paritaprevir/ritonavir tablets with AV1 printed on one side containing 12.5mg/75mg/50mg drug substance respectively copackaged with 2 beige film coated dasabuvir tablets with AV2 printed on one side containing 270.26 mg of dasabuvir sodium hydrate equivalent to 250 mg dasabuvir base. Ombitasvir, paritaprevir and ritonavir drug substance are each formulated (b) (4) at **AbbVie** (b) (4) before being further processed into the final tablets at **AbbVie Inc.** in **North Chicago, IL**. Ritonavir Tablets (NDA 22417) utilize (b) (4) AbbVie is the Applicant for both this NDA and NDA 22417.

Ombitasvir, paritaprevir and dasabuvir are all New Molecular Entities (NME) and cross-referenced to other AbbVie held INDs. The dasabuvir tablet is manufactured at **AbbVie Ireland** in **Sligo, Ireland**. Several additional sites and companies have been listed as excipient testing and packaging facilities for Viekira Pak; both domestic and international.

The quality of the drug products are controlled by tests for description, identity, assay, (b) (4) content uniformity, degradation products, and dissolution. (b) (4)

The commercial container closure system is a push through aluminum blister pack within a cardboard wallet and then packaged as a seven day supply in a cardboard carton. The Applicant is requesting 24 months of expiration dating and it is supported by 15 and 12 months of registration stability data for the dasabuvir and combined drug substance tablet respectively, in addition to multiple supportive studies including, site specific, stability challenging, (b) (4) stability, and tablets manufactured (b) (4)

Drug Substances:

Dasabuvir

Dasabuvir is a new molecular entity. The drug substance, dasabuvir sodium, is a white to pale yellow to pink powder. The drug substance is manufactured as monosodium salt monohydrate (b) (4) (b) (4)
Dasabuvir sodium is not hygroscopic and has low solubility by BCS criteria. Dasabuvir has no chiral centers and is optically inactive. (b) (4)

The dasabuvir sodium drug substance is manufactured (b) (4)

The specifications for dasabuvir sodium drug substance includes tests for description, identification, assay, impurities, sodium content, residual solvents, (b) (4) water content, residual heavy metals, and microbiological quality. As revised, the acceptance criteria for the tests are acceptable to ensure identity and quality of the drug substance. The proposed commercial scale batch is about (b) (4) kg. Satisfactory batch analysis data from 20 batches of the drug substance manufactured on

scales ranged from (b) (4) Kg are provided. At the time of the NDA submission, 12 months long term and 6 months accelerated stability data were provided, along with up to 48 months data from supportive batches to support the retest period of (b) (4) months proposed for the dasabuvir sodium drug substance.

Ritonavir

Ritonavir is used as a pharmacokinetic enhancer in Ombitasvir/Veruprevir/Ritonavir Film-Coated Tablets. AbbVie incorporates ritonavir drug substance CMC information into this NDA as agreed by FDA by cross-reference to previously submitted information in AbbVie's Norvir Oral Solution NDA (20-659). As requested by FDA, AbbVie includes a single drug substance element in Module 3 to clarify that all drug substance information is cross-referenced to the Norvir NDA. No substantial review on Ritonavir drug substance is carried out during this review cycle.

Paritaprevir

Paritaprevir drug substance is white to off-white powder with very low water solubility. Paritaprevir is manufactured (b) (4) as a dihydrate. (b) (4) Paritaprevir is manufactured (b) (4) The control strategy used ensures process performance and drug substance quality. (b) (4)

Paritaprevir drug substance has low aqueous solubility and moderate permeability. These drug substance characteristics require a (b) (4) formulation. The final drug product delivers paritaprevir (b) (4) using a (b) (4) manufacturing process.

The drug substance specifications include tests for description, identification, (b) (4) assay, impurities, genotoxic impurities, residue on ignition, water and microbiological attributes. Twelve months of long-term and 6 months accelerated stability data were provided at the time of NDA submission. The data supports a retest period of (b) (4) months when stored below (b) (4) °C.

Ombitasvir

Ombitasvir drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. It is manufactured (b) (4) as a 4.5 hydrate. (b) (4) Ombitasvir drug substance is manufactured (b) (4)

(b) (4) The manufacture of ombitasvir uses a traditional control strategy. (b) (4)

Ombitasvir has very low aqueous solubility of 0.01 to 0.5 µg/mL over the physiological pH range. (b) (4)

The drug substance specifications include tests for description, identification, (b) (4) assay, impurities, genotoxic impurities, carcinogenic impurities, residue on ignition, water and microbiological attributes. Twelve months of long-term and 6 months accelerated stability data were provided at the time of NDA submission. The data supports a retest period of (b) (4) months when stored below (b) (4) °C.

B. Description of How the Drug Product is Intended to be Used

VIEKIRA PAK (ombitasvir, paritaprevir and ritonavir tablets copackaged with dasabuvir tablets), 12.5mg/75mg/50mg and 250mg orally administered tablet therapy for the treatment of chronic HCV GTI infection in adults. VIEKERA PAK is a copackaged 4 tablet therapy in which two pink ombitasvir/paritaprevir/ritonavir tablets and one beige dasabuvir tablet are taken in the morning (A.M.) followed by one beige dasabuvir tablet taken in the evening (P.M.). All tablets are to be taken orally with food. The daily tablet combination is packaged in a blister pack in a wallet configuration design with instructions for daily use. Seven wallet VIEKIRA PAKs are then packaged in a secondary carton for weekly use. The product should be stored at or below 30ºC (86ºF).

Dasabuvir Tablet

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	(b) (4)				
Physical stability (solid state)					
Content uniformity					
Microbial limits					

	(b) (4)
Dissolution – BCS Class II & IV	
Impurities	
Particle size of drug substance	

Ombitasvir, Paritaprevir and Ritonavir Tablet

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Stability	(b) (4)				
Physical stability (b) (4)					
Content uniformity					
Microbial limits					

Dissolution – BCS Low Solubility	(b) (4)
Impurities	
Particle Size of Drug Substance	

C. Basis for Not-Approvability Recommendation

Sufficient information has been provided in the NDA to assure the quality of the drug substances and the drug product. Product Quality Microbiology has recommended approval of the NDA. The Biopharmaceutics review is pending, but the reviewer has indicated that the dissolution method and specifications are acceptable. However, the NDA is not recommended for approval at this time due to the following,

- A CMC information request is currently outstanding
- The Office of Compliance has not yet made an Overall Acceptable site recommendation
- Finalization of the labeling is pending team review

The NDA can be recommended for approval upon resolution of the pending issues.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	Maotang Zhou, PhD	19-SEP-2014
	Milton Sloan, PhD	19-SEP-2014
	Caroline Strasinger, PhD	19-SEP-2014
ChemistryTeamLeaderName/Date:	Stephen Miller, PhD	19-SEP-2014
ProjectManagerName/Date:	Althea Cuff	19-SEP-2014

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

/s/

CAROLINE STRASINGER
09/19/2014

MAOTANG ZHOU
09/19/2014

MILTON J SLOAN
09/19/2014

RAPTI D MADURAWE
09/19/2014

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **206619**

2. DATES AND GOALS:

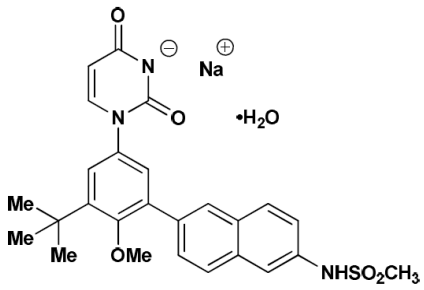
Letter Date:	Submission Received Date : Apr 21, 2014
PDUFA Goal Date: Dec 21, 2014	Primary Reviews signed off in DARRTS: Sept 21, 2014

3. PRODUCT PROPERTIES:

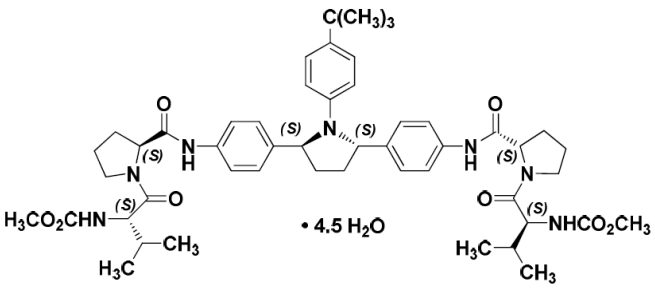
Trade or Proprietary Name:	Pending
Established or Non-Proprietary Name (USAN):	Ombitasvir, ABT-450 and Ritonavir Tablets 12.5mg/75mg/50mg Copackaged with Dasabuvir Tablets 250mg
Dosage Form:	Copackage of both types of tablets (2 of each per day)
Route of Administration	Oral
Strength/Potency	As above
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of Chronic Hepatitis C infection

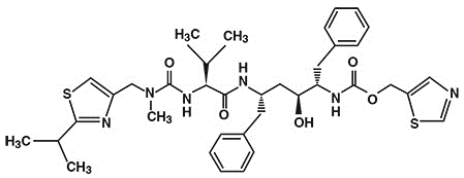
5. DRUG SUBSTANCE STRUCTURAL FORMULA:



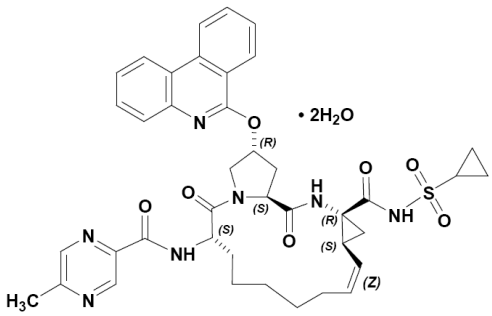
Dasabuvir sodium
ABT-333



Ombitasvir
ABT-267



Ritonavir



"Paritaprevir" USAN Pending (ABT-450)

6. NAME OF APPLICANT (as indicated on Form 356h):

AbbVie

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (6 mo + 2 mo under PDUFA-V)
Submission Classification (Chemical Classification Code):	Type 1 (New Molecular Entity) Type 4 (new combination – not previously approved in the US)
Application Type:	505(b)(1)
Breakthrough Therapy	Yes
Responsible Organization (Clinical Division):	DAVP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation	X		
Environmental Assessment		X	< 1ppb for all (Ritonavir projected at (b) (4) kg/yr)
CDRH		X	
Other			

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes No
CMC Filing Issues:
1.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes
CMC Comments for 74-Day Letter:
1. We note that you have cross-referenced all CMC information on ritonavir drug substance to NDA 20-659. However, a cross-reference is not generally appropriate for the following information, which we recommend you directly included in the application: • Physical or chemical attributes of the drug substance which are important for dosage form performance (e.g., characterization; justification of specification; etc.) • The specification that is used for acceptance of the drug substance • The analytical methods that will be used for acceptance of the drug substance • Complete information on the manufacturing, release or stability testing, packaging, or labeling facilities for the drug substance 2. Clarify the intended use of the (b) (4). 3. **Hold until USAN adopts new name (estimated July 30):** Please update NDA sections 2.3.S.1 and 3.2.S1 for the ABT 450 drug substance with appropriate USAN nomenclature.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Biopharmaceutics Filing Issues:
1.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? No
Biopharmaceutics Comments for 74-Day Letter:
1.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Microbiology Filing Issues:
Dr. Pfeiler's Microbiology Filing Review in DARRTS (May 6, 2014) recommends approval for this NDA.

APPEARS THIS WAY ON ORIGINAL

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
	X		

Is a team review recommended?	Yes
Suggested expertise for team:	
Milton Sloan	(ABT-450 and Ombitasvir drug substances)
Maotang Zhou	(Dasabuvir and Ritonavir drug substances)
Caroline Strasinger	(both drug products)
Elsbeth Chikhale	(Biopharmaceutics)
Angelica Dorantes	(Biopharmaceutics Secondary Review)
Erika Pfeiler	(Prod Qual Micro) – Review Complete
Rapti Madurawe	(Secondary Review)
Althea Cuff	(ONDQA PM)
Katie Schumann	(DAVP PM)

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Biopharmaceutics Summary of Critical Issues and Complexities

Submission:
The Applicant is seeking approval of a 505(b)(1) New Drug Application (NDA) for a fixed dose combination (FDC) film coated tablet containing 75 mg ABT-450, 50 mg ritonavir, and 12.5 mg ombitasvir (ABT-267), co-packaged with a film coated tablet containing 250 mg dasabuvir (ABT-333), indicated for the treatment of genotype-1 chronic hepatitis C infection, including patients with cirrhosis.

The Applicant has developed 3 new molecular entities (NMEs) which are all direct-acting antiviral agents (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection: ABT-450 (dosed with ritonavir as a pharmacokinetic enhancer; combination denoted as ABT-450/r), ABT-267, and ABT-333. The formulations of the two co-packaged tablets are provided in Appendix 1, below.

The FDC ombitasvir/ABT-450/ritonavir tablet [redacted] (b) (4) form the final tablet. [redacted] (b) (4)

The ABT-333 tablet contains dasabuvir [redacted] (b) (4) in the form of a monohydrate was selected for drug product development [redacted] (b) (4)

During the development of the FDC tablet and the ABT-333 tablet, a variety of investigational formulations have been used. Some of these investigational formulations have been linked by in vivo relative bioavailability (BA) and/or bioequivalence (BE) studies.

A schematic diagram of all formulations used in the drug development is shown below.

(b) (4)

[redacted]

Review: The Biopharmaceutics review of this NDA will be focused on the evaluation of:

- The proposed dissolution methods and acceptance criteria for each active and each tablet.
- Overall assessment of the in vitro and in vivo bridging studies conducted throughout the development of the two proposed products with three NMEs
- Evaluation of the BE study M14-196 supporting the bridging of the clinically tested ABT-333 tablet manufactured at AbbVie, North Chicago, USA and the to-be-marketed ABT-333 tablets manufactured at Sligo, Ireland.
- In addition, the clinical pharmacology reviewer (OCP) has requested that ONDQA-Biopharmaceutics help with the review of the following 3 RBA/BE studies: M12-683, M13-391, and M13-331.

Since none of the PK studies is a pivotal BE study on which overall approval is based on, a request to OSI for an inspection of the clinical and analytical sites of the above BA/BE studies is NOT needed.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		IND 10326 docs shared with review team: FDA responses and Abbvie withdrawal of (b) (4) proposal FDA meeting minutes of Sept 2013 CMC meeting (DS controls; control of (b) (4) dissolution) AbbVie's responses to CMC feedback on CMC issues including DS and DP stability and start of shelf life (at July 2013 multidisc PreNDA mtg)

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		Apr 29 356h

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		Categorical exclusion for all with < 1ppb The 3 NMEs have << 1 ppb Ritonavir projected at (b) (4) kg/yr

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		A flow diagram and a narrative description of the manufacturing process are provided for dasabuvir
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		(b) (4) intermediates are identified, and critical process parameters are identified (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		Dasabuvir: 12 mos long term and 6 mos accelerated data for three primary batches; Up to 48 mos data for batches made from a previous process
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		Dasabuvir: Identify DS CQAs; Identify Critical material attributes and CPPS; Use process knowledge and quality risk management to establish control strategies; No RTRT proposed. Some tests such as (b) (4) content and GTIs are not included in DS specification based on control strategies and process understanding Ombitasvir and "paritaprevir": A list of key elements in the control strategy is provided for each DS. The CQAs and associated CPC are provided. Also, information on CQAs for the DS linked to the DP CQAs are provided.
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		A description and flow diagram for each DP are included. Unexecuted batch records for (b) (4) both DP at commercial scale are included Executed batch records for the Primary Stability Batch for both DP
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Several formulations were investigated for each tablet. A table with the respective formulations and the stage of clinical trial has been provided in the submission 3.2.P.2 for each tablet.
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		Single use blister (b) (4) with push through 0.020 mm aluminum foil lidding, (b) (4)
24.	Does the section contain controls of the final drug product?	X		Attached below

25.	Has stability data and analysis been provided to support the requested expiration date?	X		Dasabuvir Tablets 15 months long term (30°C/75%RH) on primary stability batches ((b) (4) commercial scale) 6 mo 3 lots at site specific long-term ((b) (4) scale) accelerated data (40°C/75%RH) are provided on two batches Ombitasvir and ABT-450/Ritonavir Tablets 12 months long term 3batches ((b) (4) scale) (30°C/75%RH) accelerated data (40°C/75%RH) are provided on two batches 24 mo expiry is proposed for "Store at or below 30°C."
26.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
28.	Is there a methods validation package?	X		Section 3.2.R

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	Apr 2, 2014	
Seven LOAs for packaging components					

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		Blister for single, and carton for single, 7 day and 28 day blister, (b) (4)

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
33.	Does the application contain dissolution data?	☒	☐	
34.	Is the dissolution test part of the DP specifications?	☒	☐	Proposed method for ABT-333 Tablet (RTM.C5103): Apparatus 2 (paddle), 900 mL of 0.05M phosphate buffer, pH 6.8 with 15 mM hexadecyltrimethylammonium bromide at 37°C, and 75 rpm Proposed acceptance criterion for ABT-333 Tablet: Q= (b) (4)% at 15 minutes Proposed method for FDC Tablet (RTM.C5203): Apparatus 2 (paddle), 900 mL of 0.05M sodium phosphate buffer, pH 6.8 with 0.3% (w/v) polyoxyethylene 10 lauryl ether (or equivalent decaethylene glycol mono dodecyl ether) at 37°C, and 75 rpm Proposed acceptance criterion for FDC Tablet: Q= (b) (4)% at 180 minutes for all 3 actives
35.	Does the application contain the dissolution method development report?	☒	☐	Dissolution method development reports are provided in section 3.2.P.2.2 for each drug product.
36.	Is there a validation package for the analytical method and dissolution methodology?	☒	☐	See section 3.2.P.5.3 for each drug product
37.	Does the application include a biowaiver request?	☐	☒	
38.	Does the application include an IVIVC model?	☐	☒	
39.	Is information such as BCS classification mentioned, and supportive data provided?	☐	☒	

40.	Is information on mixing the product with foods or liquids included?	☐	☒	
41.	Is there any in *vivo* BA or BE information in the submission?	☒	☐	Several BA and/or BE studies are performed. See section 5.3.1
FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
42.	**ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	☒		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A (fileable)
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A (fileable)
45.	Are there any potential review issues identified?	☒	☐	See "Overall Filing Conclusions and Recommendations" section, above

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Appendix 1. Composition of Drug Product

Composition of Dasabuvir Tablets, 250 mg

Component	Quality Standard	Function	Amount (mg)/Tablet
(b) (4)			
Dasabuvir Sodium	In-house	Active	270.26
Microcrystalline Cellulose (b) (4)	NF/Ph. Eur.	(b) (4)	
Microcrystalline Cellulose (b) (4)	NF/Ph. Eur.		
Lactose Monohydrate	NF/Ph.Eur.		
(b) (4) Copovidone	NF/Ph. Eur.		
Croscarmellose Sodium	NF/Ph. Eur.		
Colloidal Silicon Dioxide / Anhydrous Colloidal Silica	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
(b) (4)			
Film-Coating			
(b) (4)			

(b) (4)

Composition of Ombitasvir, ABT-450 and Ritonavir Tablets, 12.5mg / 75mg / 50mg

Component	Quality Standard	Function	Amount (mg)/Tablet
			(b) (4)
Ombitasvir	In-house standard	Active	12.5
Copovidone, K value 28	NF/Ph. Eur. and In-house standard		(b) (4)
Vitamin E Polyethylene Glycol Succinate	NF and In-house standard		
Colloidal Silicon Dioxide/ Colloidal Anhydrous Silica	NF/Ph. Eur.		
			(b) (4)
ABT-450	In-house standard	Active	75.0
			(b) (4)
Propylene Glycol Monolaurate Type I	NF/Ph. Eur.		(b) (4)
			(b) (4)
Ritonavir	USP/Ph. Eur.	PK Enhancer	50.0
	(b) (		(b) (4)
Sorbitan Monolaurate	NF/Ph. Eur.		
			(b) (4)
Sodium Stearyl Fumarate	NF/Ph. Eur.		
Film-Coating			
			(b) (4)

(b) (4)

Appendix 2. DP Specification

Table 1. Specification for Dasabuvir Film-Coated Tablets

Test	Analytical Procedure	Acceptance Criteria	Limit Type
Description Physical Description Appearance Marking Shape Color Coating	Visual	 Meets Requirements Tablet Debossed "AV2" on one side Ovaloid Beige Coated	Shelf-life
Identification, Dasabuvir (by HPLC)	RTM.C5105	(b) (4)	Shelf-life
Identification, Dasabuvir Sodium (by IR)	RTM.P1156		Shelf-life
Assay, Dasabuvir	RTM.C5105		Shelf-life
Uniformity of Dosage Units	Weight Variation	USP <905>/Ph. Eur. 2.9.40	Shelf-life
(b) (4)		≤ (b) (4)	Release Shelf-life
Degradation Products, Individual Unspecified	RTM.C5104	≤	Shelf-life
Degradation Products, Total		≤	Shelf-life
Dissolution	RTM.C5103	Q = (b) (4) at 15 minutes As per USP <711>, Acceptance Table 1/ Ph. Eur. 2.9.3, Table 2.9.3.-1	Shelf-life

LC = label claim

Table 1. Specification for Ombitasvir/ABT-450/Ritonavir Film-Coated Tablets

Test	Analytical Procedure	Acceptance Criteria	Limit Type
Description Physical Inspection Appearance Marking Shape Color Coating	Visual	Meets Requirements Tablet Debossed "AV1" on one side Oblong, biconvex Pink Coated	Shelf Life
Identification, HPLC Ombitasvir	RTM.C5199	(b) (4)	Shelf Life
Identification, HPLC ABT-450			Shelf Life
Identification, HPLC Ritonavir			Shelf Life

Table 1. Specification for Ombitasvir/ABT-450/Ritonavir Film-Coated Tablets (continued)

Test	Analytical Procedure	Acceptance Criteria	Limit Type
Identification, TLC, Ombitasvir	RTM.C5283	(b) (4)	Shelf Life
Identification, TLC, ABT-450			Shelf Life
Identification, TLC, Ritonavir			Shelf Life
Assay Ombitasvir, ABT-450 Ritonavir	RTM.5199	(b) (4)	Shelf Life
Uniformity of Dosage Units, Ombitasvir ABT-450 Ritonavir	RTM.C5221	As per USP <905> / Ph. Eur. 2.9.40 As per USP <905> / Ph. Eur. 2.9.40 As per USP <905> / Ph. Eur. 2.9.40	Shelf Life
		(b) (4)	Release Shelf life

LC = label claim

Appendix 3. Container Labels

1-Month Blister Pack Carton:
Each box contains: 4 weekly cartons of therapy, each containing 7 blisters of 4 tablets each

1-Week Blister Carton:
Each carton contains 28 tablets in 7 blisters for 1 week of treatment

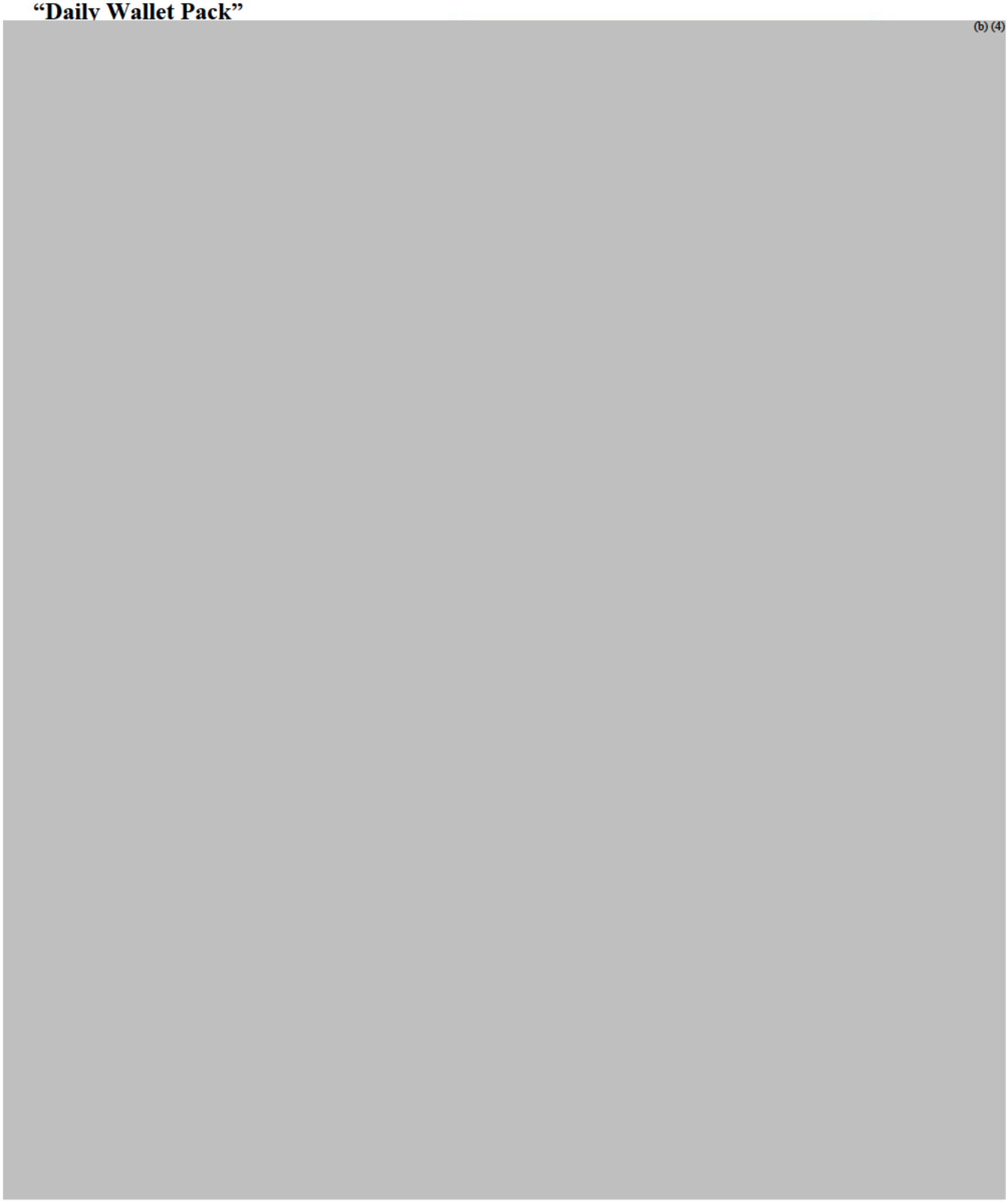
1-Month Wallet Pack Carton:
Each box contains: 4 weekly cartons of therapy, each containing 7 wallets of 4 tablets each

(b) (4)

(b) (4)

"Daily Wallet Pack"

(b) (4)



Wallet Instruction Card

(b) (4)

(b) (4)

(b) (4)

Appendix 4. DS Specification

Table 1. Specification for Dasabuvir Sodium Drug Substance

Test	Analytical Procedure	Acceptance Criteria
Description Appearance Color	Visual	 Powder, may contain lumps White to off white to light yellow to light pink to pink
Solution Test Clarity Color	Ph. Eur. 2.2.1 / 2.2.2 (b) (4)	 Clear (b) (4) Not more intensely colored than (b) (4)
Identification, Dasabuvir (by HPLC)	RTM.C4977	(b) (4)
Identification, Dasabuvir (by IR)	USP <197A>	
Identification, Counterion (Sodium)	USP <191>	USP <191>
(b) (4)		(b) (4)
Assay, Dasabuvir	RTM.C4977	
Impurity, (b) (4)	RTM.C4979	(b) (4)
Impurity, (b) (4)		
Impurity, Unspecified Identified		
Impurity, Unspecified Unidentified		
Impurities, Total		

Test	Analytical Procedure	Acceptance Criteria
Residual Solvent, (b) (4)	RTM.C4978	(b) (4)
Residual Solvent, (b) (4)		
Residual Solvent, (b) (4)	RTM.C4986	
Microbiological Quality Total AMC Total Yeast and Molds	USP <61>/Ph. Eur. 2.6.12	 (b) (4) NMT NMT

Table 2: Specification for ~~Veruprevir~~ Drug Substance (ABT 450, "Paritaprevir")

Test	Analytical Procedure	Acceptance Criteria
Description Appearance Color	Visual	 Powder, may contain lumps White to off-white
Solution Clarity Color	Ph. Eur. 2.2.1 / 2.2.2 (b) (4)	Clear (b) (4) Not more intensely colored than (b) (4)
Identification, Veruprevir (by HPLC)	RTM.C5139	(b) (4)
Identification, Veruprevir (by IR)	USP <197A>	
(b) (4)		
Assay, Veruprevir	RTM.C5139	
Impurity, (b) (4)	RTM.C5140	≤ (b) (4)
Impurity, (b) (4)		≤
Impurity (b) (4)		≤
Impurity, (b) (4)		≤
Impurity, (b) (4)		≤

Test	Analytical Procedure	Acceptance Criteria
Impurity, (b) (4)		≤ (b) (4)
Impurity, (b) (4)		≤
Impurity, (b) (4)		≤
Impurity, (b) (4)		≤
Impurity, Unspecified Identified		≤
Impurity, Unspecified Unidentified		≤
Impurities, Total		≤
Genotoxic Impurities (b) (4)	RTM.C5282	≤
Residual Solvent, (b) (4)	RTM.C5146	≤
Residual Solvent, (b) (4)		≤

Residual Solvent, (b) (4)		≤ (b) (4)
Residual Solvent, (b) (4)	RTM.C5183	≤
Residue on Ignition	USP <281>	≤
Water	USP <921>, method 1c (Extraction time of (b) (4) seconds)	≥
Microbiological Quality Total Aerobic Microbial Count Total Combined Yeasts and Molds Count	USP <61>/Ph. Eur. 2.6.12	 ≤ ≤

Table 3. Specification for Ombitasvir Drug Substance (ABT-267)

Test	Analytical Procedure	Acceptance Criteria
Description Appearance Color	Visual	Powder, may contain lumps White to off-white to light pink to light yellow
Solution Test Clarity Color	Ph. Eur 2.2.1 / 2.2.2 (b) (4)	Clear (b) (4) Not more intensely colored than reference solution (b) (4)
Identification (by HPLC)	RTM.C5258	(b) (4)
Identification (by IR)	USP <197A>	
(b) (4)		
Assay, Ombitasvir	RTM.C5258	
Impurity, (b) (4)	RTM.C5259	≤
Impurity, (b) (4)		≤
Impurity, (b) (4)		≤
Impurity, (b) (4)		≤

a. (b) (4) (b) (4)

Table 3. Specification for Ombitasvir Drug Substance (continued)

Test	Analytical Procedure	Acceptance Criteria
Impurity, (b) (4)	RTM.C5259	≤ (b) (4)
Impurity, Unspecified Identified		≤
Impurity, Unspecified Unidentified		≤

Impurities, Total (b) (4)		≤	(b) (4)
Genotoxic Impurities (b) (4)	RTM.C5263	≤	
Carcinogenic Impurity (b) (4)	RTM.C5264	≤	
Residual Solvent (b) (4)	RTM.C5260 Alternate: RTM.C5453	≤	
Residue on Ignition	USP <281>	≤	
Water Content	USP <921> Method 1c	≤	
Microbiological Quality Total Aerobic Microbial Count Total Yeasts and Molds Count	USP <61>/Ph. Eur. 2.6.12	 ≤ ≤	

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/s/

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06/14/2014
NDA is fileable from the CMC and Biopharm perspectives.

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