CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208624Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208624
Review 1

Drug Name/Dosage Form	Viekira XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) Extended-Release Tablets
Strength	200mg/8.33mg/50mg/33.33mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Sept 28, 2015	Multiple
Amendment	Feb 5, 2016	Quality
Amendment	Feb 19, 2016	Quality
Amendment	Mar 8, 2016	Quality
Amendment	Mar 30, 2016	Quality
Amendment	June 10, 2016	Quality
Amendment	June 14, 2016	Labeling

Quality Review Team

Discipline	Reviewer	Secondary Reviewer
ATL	Stephen Miller	
RBPM	Florence Aisida	
Drug Substance	Stephen Miller	Bala Shanmugam
Drug Product	Shirkant Pagay	Bala Shanmugam
Biopharmaceutics	Jing Li	Elsbeth Chikhale
Process	Christine Falabella	Upinder S Atwal,
Facilities	Frank Wackes	Mahesh Ramanadham

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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 *(if applicable)*		(b)(4)	Adequate *	11/5/2015	Reviewed by R. Agarwal
	Type III *(if applicable)*			Information in the NDA*	-	
	Type III			Information in the NDA*	-	

- The same packaging components were used in NDA 206619; no stability issues were encountered.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Reviews of original NDA	NDA 206619	Closely related tablet
Reviews of original NDA	NDA 20659	Review of ritonavir drug substance
Reviews of original NDA	NDA 22417	Review of ritonavir (b)(4)

2. CONSULTS:

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

Executive Summary

I. Recommendations

All reviews and inspectional activities related to product quality have been completed, and this NDA is recommended for approval.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues NA
2. Action letter language, related to critical issues such as expiration date: None
3. Benefit/Risk Considerations. This application's main focus was to improve patient compliance and acceptability by development of once daily dosing. Otherwise there are no specific benefit/risk considerations associated with this modified-release solid-oral dosage form.

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

II. Summary of Quality Assessments

1) Drug Substance Quality Summary

- All information on Dasabuvir, Ombitasvir, and Parataprevir drug substances are cross-referenced to the approved NDA 206619
- All information on Ritonavir drug substance is cross-referenced to the approved NDA 20659
- The controls on drug substance quality established for those referenced NDAs are appropriate for drug substances used to produce this product.

2) Drug Product [Established Name] Quality Summary

- The formulation (bilayer tablet; extended release for dasabuvir; reduced dosing frequency compared to Viekira Pak) was designed to improve patient compliance and acceptability.
- Ombitasvir, paritaprevir and ritonavir are practically insoluble drugs. (b) (4) [redacted] All the excipients used in the formulation meet compendial(USP/NF) quality standard. Therefore both formulation and processing for this NDA can be considered as a novel approach to improve the dissolution and thereby bioavailability of these drug substances.
- [redacted] (b)(4)

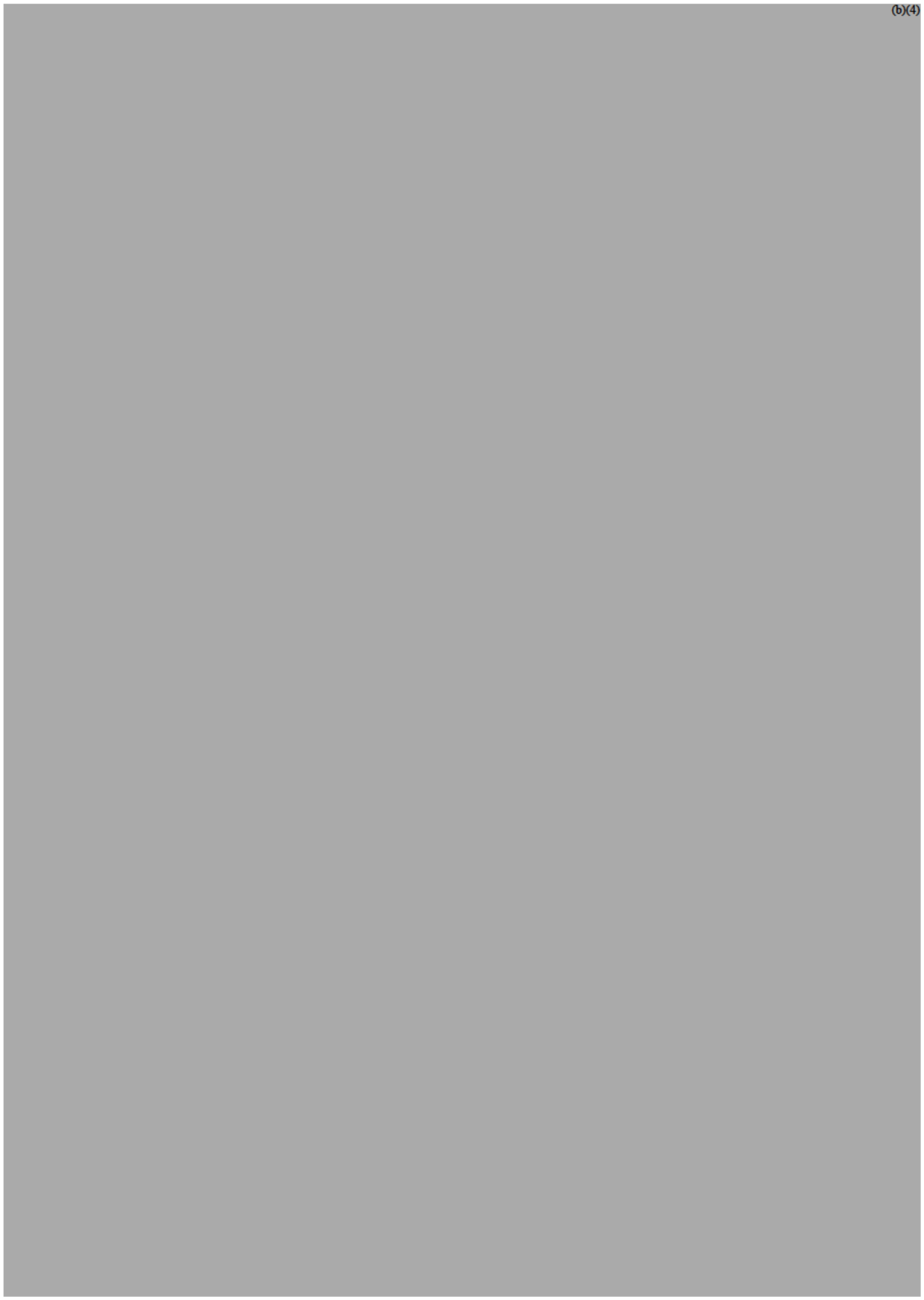
(b)(4)

- Excipient quality controls are in place, including additional specifications beyond the compendial requirements. Hypromellose 2208 used in dasabuvir ER tablet layer for (b)(4) is a compendial grade material. However, additional requirement set for this cellulose polymer are (b)(4) (b) (4) (b) (4) Copovidone for ombitasvir, paritaprevir and ritonovir (b)(4) is controlled for specific grade K-28 (b) (4) the drug product. Additional testing for copovidone is necessary for (b)(4) ombitasvir. (b)(4) Vitamin E.
- Controls on tablet (b)(4)

1. Strength 200mg/8.33mg/50mg/33.33mg
2. Description/Commercial Image: Pale yellow-colored, film-coated, oblong shaped tablets, debossed with "3QD" on one side
3. Summary of Product Design Film-coated bi-layer tablet (unscored)
4. List of Excipients: See Review Notes. Note that the components of the ER layer, the IR layer and the film coating are all listed separately in the Prescribing Information.
5. Process Selection (Unit Operations Summary)

(b)(4)

(b)(4)



(b)(4)

[redacted]

6. Container Closure: 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 (blister) pack contains three tablets.
7. Expiration Date & Storage Conditions: 24 months when stored at or below 30°C (86°F).
8. List of co-packaged components: (b)(4) [redacted]

3) Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Viekira XR
Non Proprietary Name of the Drug Product	Dasabuvir, ombitasvir, paritaprevir, and ritonavir extended-release tablets
Non Proprietary Name of the Drug Substance	Dasabuvir sodium monohydrate; ombitasvir; paritaprevir; ritonavir
Proposed Indication(s) including Intended Patient Population	Treatment of adult patients with chronic infection with Hepatitis C Virus (HCV)
Duration of Treatment	12-24 weeks
Maximum Daily Dose	Three tablets taken once per day
Alternative Methods of Administration	None

4) Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance: Not establsihed.
   - Drug Product: Not established.

2. Biowaivers/Biostudies:
   - Biowaiver Requests: This application does not contain a biowaiver request.
   - PK studies: The PK studies are reviewed by the Office of Clinical Pharmacology.
   - IVIVC: A Level (b)(4) IVIVC was attempted but not established.

3. Dissolution method:
   The following dissolution method is found acceptable:

Apparatus	Apparatus 3
Agitation	25 dpm
Medium	15 mM CTAB in 0.03M sodium phosphate buffer, pH 6.8
Volume	250 mL/ vessel
Temperature	37 °C
Analytics	HPLC –UV (252nm for ombitasvir, 280 nm for paritaprevir, 240 nm for ritonavir, 320 nm for dasabuvir)

4. Dissolution acceptance criteria:
   The following revised dissolution acceptance criteria are found acceptable:

For the IR layer (Ombitasvir/ Paritaprevir/ Ritonavir):

Time (min)	% dissolved
30 min	NMT (b)(4) %
90 min	NLT (b)(4) %

For the ER layer (Dasabuvir):

Time (hr)	% dissolved
3 hr	(b)(4) %
9 hr	(b)(4) %
18 hr	NLT (b)(4) %

5. Theoritical risk of alcohol induced dose dumping

- In vitro dissolution data showed that addition of 40% alcohol in 0.1 N HCl induced a slight increase in the release rate for dasabuvir in the ER layer as well as the APIs in the IR layer.
- The alcohol induced dose dumping is prevented by restraining the consumption of alcohol. The package insert stated in section 2.2 that "For optimal release of dasabunir, alcohol should not be consumed within 4 hours of taking VIEKIRA XR".

From a Biopharmaceutics perspective, NDA 208624 for Dasabuvir/ Ombitasvir/ Paritaprevir/ Ritonavir tablets (200 mg/ 8.33 mg/ 50 mg/ 33.33 mg) is recommended for approval.

5) Novel Approaches NA

6) Any Special Product Quality Labeling Recommendations

a) At the appropriate time, the applicant should submit revised container labels that incorporate these recommendations:
   i) The product name on the container labels should use this language:

Viekira XR
(dasabuvir, ombitasvir, paritaprevir, and ritonavir)
Extended-Release Tablets
200 mg / 8.33 mg / 50 mg / 33.33 mg

ii) Include the salt equivalence statement: Each VIEKIRA XR tablet contains 200 mg of dasabuvir equivalent to 216 mg of dasabuvir sodium monohydrate, 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir

iii) OPQ supports all recommendations pertaining to the container labesl which are in Dr. Calderon's DMEPA review.

b) Add "Do not split, crush or chew tablets' at appropriate place(s) in the PI and the container labels.

7) Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

NDA 208624 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: 2016.06.24 10:44:35 -04'00'

Stephen Miller, Ph.D.
CMC-Lead (QAL); Branch 3; Division of New Drug Products I; ONDP
Office of Pharmaceutical Quality; CDER; FDA

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

All facility evaluations are complete and acceptable.

Final Recommendation:
APPROVAL

Entered by Frank Wackes, 05/30/2016

Secondary Review Comments and Concurrence:

Derek S Smith, Ph.D., 05/30/2016

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

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

Yes. The proposed in vitro dissolution test is adequate for quality control. The selection of the dissolution conditions (e.g., medium, surfactant, apparatus, rotation speed, etc.) was adequately justified. The discriminating ability of the dissolution method was demonstrated. The method was validated. The proposed acceptance criteria are supported by the dissolution data for the clinical and primary stability batches.

38.1. Solubility:

As summarized in Table 38-1, the solubility of the APIs is low in aqueous solution. The solubility profiles for ombitasvir and dasabuvir as a function of pH are presented in Figures 38-1.

Table 38-1 Physicochemical properties of the APIs

	pKa(s)	Solubility
Dasabuvir	8.2, 9.2	Poor solubility throughout the physiological pH range of 1.0 to 7.4 (~0.15 µg/mL at pH 7.4)
Ombitasvir	2.5	poor aqueous solubility throughout the physiological pH range of 1.0 to 7.4 (approximately 0.5 µg/ mL at pH 1.0 and approximately 0.02 µg/ mL at pH 6.8)
Paritaprevir	4.6	poor aqueous solubility throughout the physiological pH range of 1.0 to 7.4 (< 0.09 µg/ mL at pH 2.0 and approximately 12 µg/ mL at pH 6.8)
Ritonavir	2.8	pH dependent with solubility values of approximately 510 µg/mL in 0.1 N HCl and approximately 2 µg/mL at pH ≥ 4

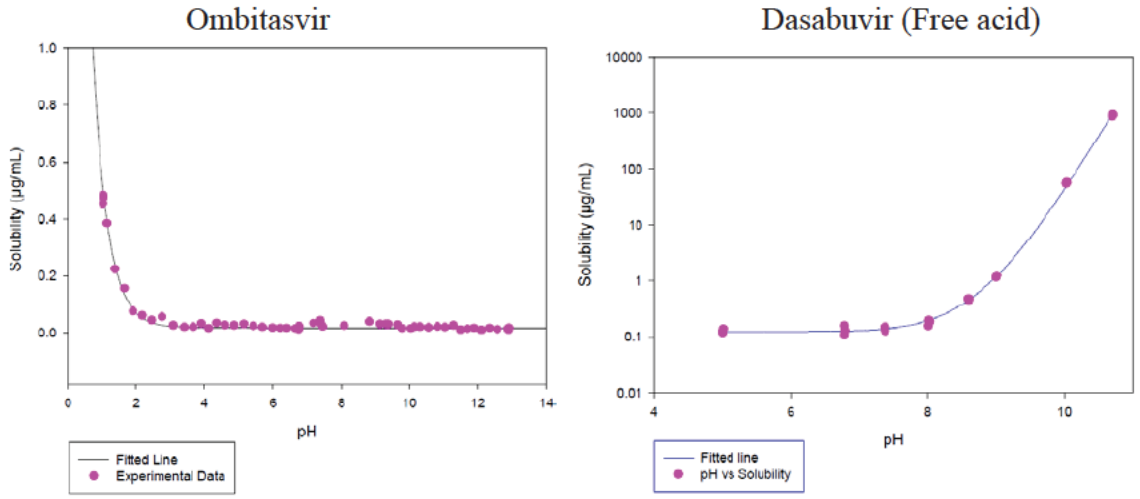

Figure 38-1 Solubility of Ombitasvir and Dasabuvir at 25 °C as a function of pH

38.2. Formulation:

Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir Film-Coated (3QD) Tablet is a bilayer tablet consisting of an extended release (ER) layer and an immediate release (IR) layer. The IR layer is composed of [redacted] ombitasvir, paritaprevir and ritonavir, which are identical to that used in the approved Ombitasvir/Paritaprevir/ Ritonavir Tablets. The ER layer uses hypromellose (HPMC) to [redacted]. HPMC is a commonly used excipient in matrix controlled-release tablets. The quantitative composition of the proposed 3QD Tablets is presented in Table 38-2.

Table 38-2 Composition of 3QD Tablets

Component	Quality Standard	Function	Amount mg/Tablet
ER Layer			
Dasabuvir sodium	In-house standard	Active	216.2
Copovidone, K value 28	NF/Ph. Eur.	[redacted]	[redacted]
[redacted]	USP/Ph. Eur.		
[redacted]			
Hypromellose 2208, 17,700 mPa•s	USP/Ph. Eur. and In-house standard		
Colloidal Silicon Dioxide/ Colloidal Anhydrous Silica	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
IR Layer			
[redacted]			
Ombitasvir	In-house standard	Active	8.33
Copovidone, K value 28	NF/Ph. Eur. and In-house standard	[redacted]	[redacted]
Vitamin E (Tocopherol) Polyethylene Glycol Succinate (TPGS)	NF and In-house standard		
Colloidal Silicon Dioxide/ Colloidal Anhydrous Silica	NF/Ph. Eur.		
[redacted]			
Paritaprevir	In-house standard	[redacted]	50.0
[redacted]			

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(b) (4)

[redacted]

Reviewer's Assessment of the dissolution acceptance criteria:

The following dissolution acceptance criteria were recommended based on the provided dissolution data as presented in Figures 38-12 to 38-14, and the recommendations were conveyed to the Sponsor on March 17, 2016.

2. *The provided dissolution data do not support the proposed acceptance criteria and it is not acceptable. Implement the following dissolution acceptance criteria for the 3QD tablet, and provide the revised Specification Tables with the updated acceptance criteria for the dissolution test.*

For the IR layer (Ombitasvir/ Paritaprevir/ Ritonavir):

Time (min)	*% dissolved*

30 min	*NMT* (b) (4) *%*
90 min	*NLT* (b) (4) *%*

For the ER layer (Dasabuvir):

Time (hr)	*% dissolved*
3 hr	(b) (4) *%*
9 hr	(b) (4) *%*
18 hr	*NLT* (b) (4) *%*

3. *Provide the complete dissolution profile data (individual, mean, SD, profiles) for the stability batches in ".xpt" format. Include dissolution data at all the time points you have sampled in addition to the proposed specification time points.*

In the response dated March 30, 2016, the Applicant accepted the recommended dissolution acceptance criteria and updated the drug product specifications as suggested. The requested stability dissolution data were also provided, and the data conform to the revised acceptance criteria as shown in Figure 38-14.

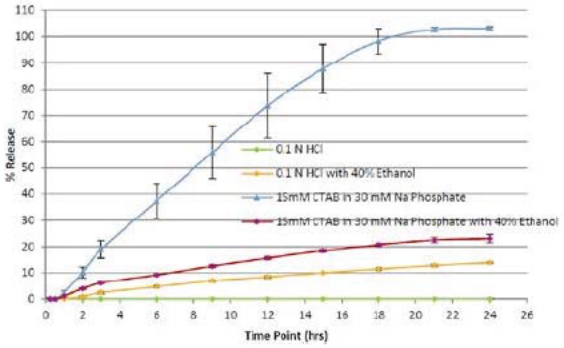
The revised dissolution acceptance criteria are acceptable and supported by the dissolution data of the primary stability batches.

38.5 Effect of Alcohol on Drug Release

The effect of alcohol on drug release was studied in order to investigate potential dose dumping from the ER layer of 3QD Tablets. The dissolution profiles have been generated in both 0.1 N HCl and in the optimal dissolution medium (Apparatus 3, 25 dpm, 30 mM sodium phosphate buffer in 15 mM CTAB, pH 6.8, with and without alcohol).

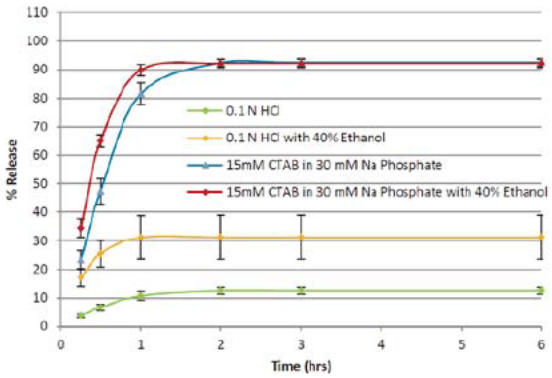
The results of the alcohol investigation are shown in Figure 38-15.

Dasabuvir



Paritaprevir

Ombitasvir



Ritonavir

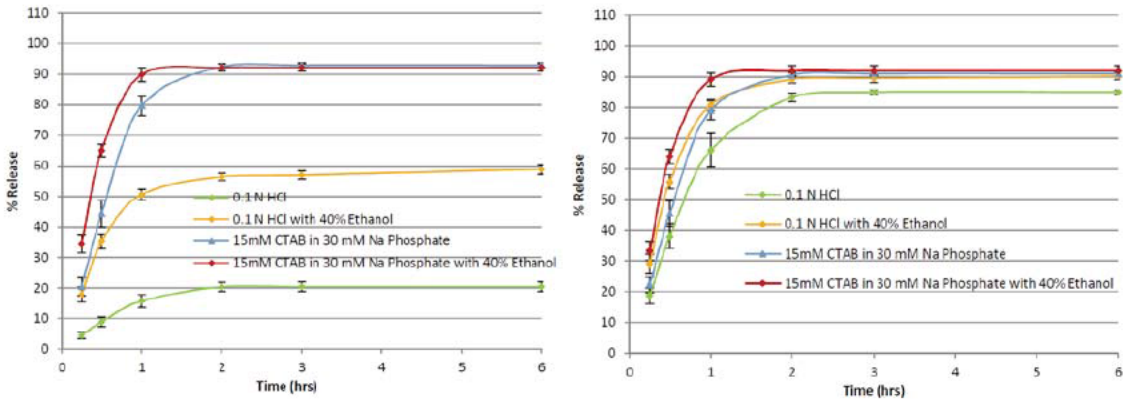


Figure 38-15 Impact of alcohol on in vitro release of 3QD tablet

Reviewer's Assessment:

The data indicates that alcohol does not induce in vitro dose dumping from the formulation when the proposed regulatory dissolution medium was used. However, there is a slight increase in release rate for dasabuvir in the ER layer as well as the APIs in the IR layer when the medium of 0.1 N HCl was used. This finding was conveyed to the Clinical Pharmacology Reviewer who might suggest labeling language regarding alcohol intake.

38.6. Extended Release Claim:

A phase I, non-fasting (fed), open-label, two-part study was conducted to compare the bioavailability of dasabuvir, ombitasvir, ABT-450 and ritonavir from the 3QD and the 3-DAA regimens. The reference and test regimens are as follows:

Reference regimen: 3-DAA regimen (Two ombitasvir/paritaprevir (ABT-450)/ritonavir (r) co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir IR tablet (250 mg) administered under non-fasted conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasted conditions in the evening for 14 days);

Test regimen: 3QD regimen (Three Quad ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/ABT-450/ ritonavir was 600/25/150/100 mg) administered in the morning under non-fasted conditions for 14 days).

The study is made up of two parts. In Part 1, all subjects received a single dose of the 3QD regimen (three tablets) of Film-Coated Quad ER-12 (Regimen A) and a single dose of the 3-DAA regimen (Regimen B) [two ombitasvir/ABT-450/r co-formulated tablets with one dasabuvir 250 mg IR tablet in the morning and one dasabuvir 250 mg IR tablet in the evening], on two occasions in a 4-period, 2-sequence replicated crossover study design.
In Part 2, all subjects received 14-day therapy of both the 3QD regimen Film-Coated Quad ER-12 (Regimen A) and the 3-DAA regimen (Regimen B), two ombitasvir/ABT-450/r co-formulated tablets with one dasabuvir 250 mg IR tablet in the morning and one

dasabuvir 250 mg IR tablet in the evening, in a two-period, randomized, crossover design.

This review will focus on part 2 of the study which provide the steady state PK profiles.

The mean plasma concentration profiles of Dasabuvir and its metabolite Dasabuvir M1 on Day 14 are presented in the Figure 38-16.

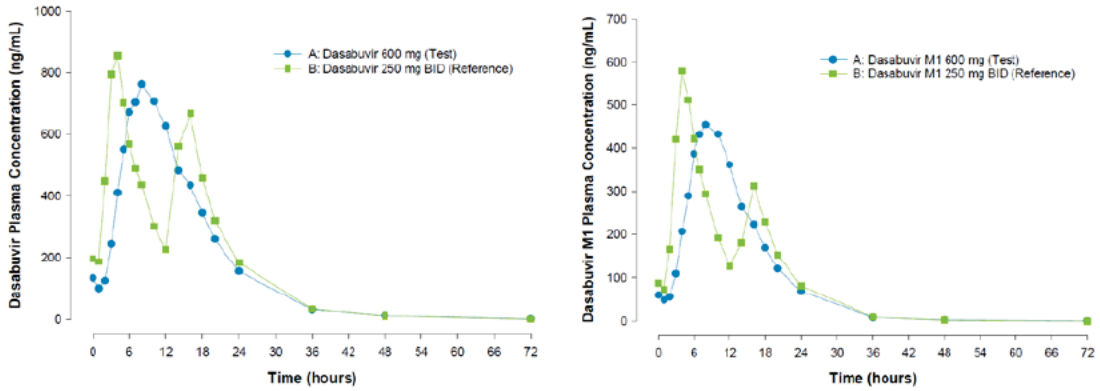


Figure 38-16 Mean plasma PK profiles for Dasabuvir and Dasabuvir M1 on day 14

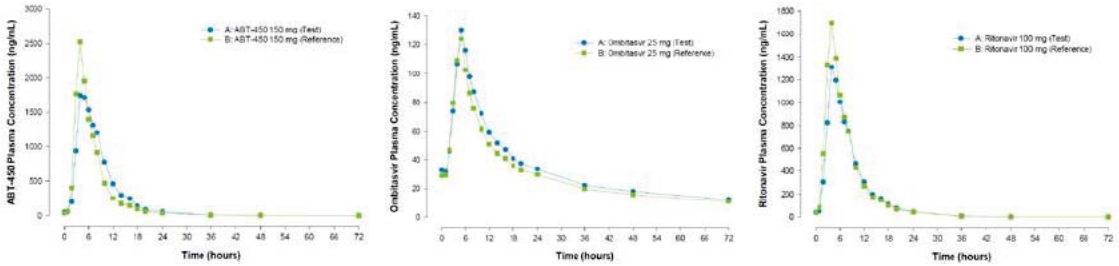


Figure 38-17 Mean plasma PK profiles for ABT-450, ombitasvir, and ritonavir on Day 14

Dasabuvir is the API in the ER component of the proposed 3QD tablets, and the ER formulation provided a delayed T_{max} for dasabuvir compared to the IR formulation, as indicated in the PK profiles and the Table below.

Table 38-8 Geometric mean PK parameters for dasabuvir and dasabuvir M1 on Day 14

Parameter (Unit)	Dasabuvir	
	Regimen A (Test) 3QD Regimen	Regimen B (Reference) 3-DAA Regimen
N	63	63
C_{max} (ng/mL)[a]	799 (896 ± 415)	879 (947 ± 357)
T_{max} (h)[b]	8.0 (4.0 – 18.0)	4.0 (2.0 – 6.0)
AUC_{24} (ng•h/mL)	8800 (10300 ± 5630)	9770 (10600 ± 4410)
C_{24} (ng/mL)	116 (155 ± 135)[d]	162 (183 ± 101)
$t_{½}$ (h)[c]	6.23 ± 1.89	5.48 ± 1.31
	Dasabuvir M1	
	Regimen A (Test) 3QD Regimen	Regimen B (Reference) 3-DAA Regimen
N	63	63
C_{max} (ng/mL)[a]	451 (527 ± 281)	562 (610 ± 241)
T_{max} (h)[b]	8.0 (4.0 – 18.0)	4.0 (3.0 – 6.0)
AUC_{24} (ng•h/mL)	4640 (5630 ± 3360)	5240 (5700 ± 2430)
C_{24} (ng/mL)	48.4 (67.9 ± 61.4)[d]	70.9 (79.8 ± 40.9)
$t_{½}$ (h)[c]	4.66 ± 1.11	4.08 ± 0.72[e]

Reviewer's Assessment:

The Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir Film-Coated (3QD) drug product was developed with the objective of providing a once-daily dosing alternative to the currently approved dosing regimen, Ombitasvir/Paritaprevir/Ritonavir Tablets (QD) and Dasabuir Tablets (BID), also referred to as the 3-DAA regimen. The 3QD Tablets are bilayer tablets consisting of an extended release (ER) layer containing dasabuvir and an immediate release (IR) layer containing ombitasvir/paritaprevir/ ritonavir.
The API in the ER layer, dasabuvir, has an active metabolite, dasabuvir M1, which was characterized as a major metabolite in human plasma. The PK analysis take both dasabuvir and dasabuvir M1 into consideration.

Study M14-566 was a two-part study to compare the bioavailability of the two regimens (3-DAA and 3QD) after a single dose and multiple doses. Part-2 of the study (steady state PK of dasabuvir and dasabuvir M1 on Day 14) was evaluated in this review for the purpose of assessing the extended release claim. This reviewer calculated the fluctuation index (FI) at steady state (Day 14) for Dasabuvir and Dasabuvir M1 using the following equation:

$$FI= (C_{max}-C_{min})/ C_{average}, \text{ where } C_{average}=AUC_{0-24}/\tau$$

As shown in the Table below, there is no significant difference in FI between the proposed ER formulation and the reference IR formulation. However the ER formulation provided significantly delayed T_{max} (8 hr versus 4 hr), which supports less dosing frequency for the ER product.

Table 38-9 Fluctuation Index Comparison

	3QD tablet (the proposed drug product with ER layer, Regimen	3-DAA tablet (IR formulation, Regimen B,

	A, Test)	Reference)
Dasabuvir	1.86±0.52	1.79±0.49
Dasabuvir M1	2.09±0.58	2.27±0.53

In addition, the presence of the [redacted](b)(4), HPMC, in the formulation, and the slow [redacted](b)(4) also suggest that the drug product is an extended release dosage form.

The above combined information supports the extended release claim.

The proposed proprietary name of "Viekira XR" is acceptable from a Biopharmaceutics perspective, based on the precedents of using XR in the trade names for other extended release drug products.

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

In total 15 ER formulations have been developed to select a [redacted](b)(4)

The ER-12 formulation was considered optimal after the development work. Upon [redacted](b)(4)

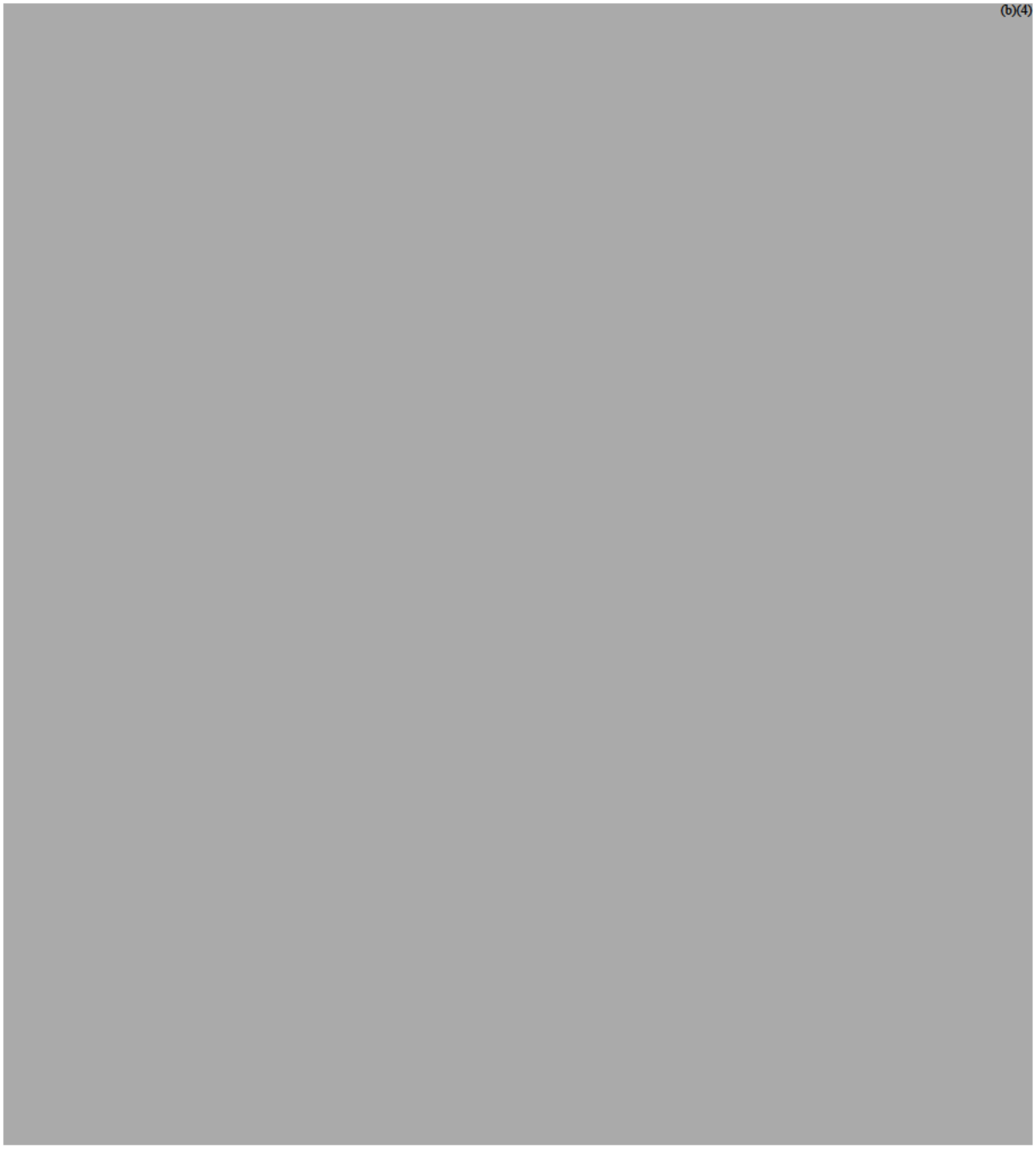
In comparison to the formulation of the pivotal BE batch, the proposed commercial formulation will have a pale yellow coating due to the [redacted](b)(4) and the tablets are debossed with "3QD" on one side. Table 39-1 shows the differences among the formulation ER-12, the pivotal batch, and the commercial batches.

Table 39-1 Formulation comparison

	ER-12	Pivotal batch	Commercial batch
[redacted](b)(4)	Yes	No	No
Color of coating	N/A	[redacted](b)(4)	Pale Yellow
Debossing	N/A	No	Yes

The coatings are identical in qualitative composition with the exception that the yellow coating does not include [redacted](b)(4) as shown in Table 39-2.

(b)(4)



(b)(4)

[redacted]

Reviewer's Assessment:

The comparative in vitro dissolution profiles adequately bridged the clinical batch and the proposed commercial batch.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From a Biopharmaceutics perspective, NDA 208624 for Dasabuvir/ Ombitasvir/ Paritaprevir/ Ritonavir tablets (200 mg/ 8.33 mg/ 50 mg/ 33.33 mg) is recommended for **APPROVAL**.

The following dissolution method and revised dissolution acceptance criteria are acceptable:

Apparatus	Apparatus 3
Agitation	25 dpm
Medium	15 mM CTAB in 0.03M sodium phosphate buffer, pH 6.8
Volume	250 mL/ vessel
Temperature	37 °C
Analytics	HPLC –UV (252nm for ombitasvir, 280 nm for paritaprevir, 240 nm for ritonavir, 320 nm for dasabuvir)
Acceptance criteria	For the IR layer (Ombitasvir/ Paritaprevir/ Ritonavir):

Time (min)	% dissolved
30 min	NMT (b)(4) %
90 min	NLT (b)(4) %

For the ER layer (Dasabuvir):

Time (hr)	% dissolved
3 hr	(b)(4) %
9 hr	%
18 hr	NLT (b)(4) %

Jing Li, Ph.D., 4/13/2016
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Concurrence and Signature:

I concur with Dr. Li's assessment and recommendation.

Elsbeth Chikhale, Ph.D., 4/19/2016
Biopharmaceutics Lead (Acting)
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Reviewer's Assessment: N/A

Please see Question #34 (Pages 144-145) in the Assessment of Process section of this review for more information.

2.3.P.7 Container/Closure System

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?

N/A

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

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)?

N/A

Reviewer's Assessment: N/A

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?

N/A

Reviewer's Assessment: **N/A**

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: **N/A**

Please see Question #34 (Pages 144-145) in the Assessment of Process section of this review for more information.

Secondary Review Comments and Concurrence: **N/A**

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

The requested action, approval of NDA 208624, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment (EA) under 21 CFR § 25.31(b) for each of the four active pharmaceutical ingredients (APIs), dasabuvir, ombitasvir, paritaprevir, and ritonavir. To the applicant's knowledge, no extraordinary circumstances exist for any of these four APIs that would warrant the preparation of an EA.

Reviewer's Assessment: Acceptable

Since this NDA will replace the same drugs in Viekira Pak (NDA (b)(4)) for the same indications , the proposal is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Adequate.

Shrikant N. Pagay, Review Completion date June 20, 2016

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D., June 23, 2016
Branch Chief (Acting), Branch 3, ONDP.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For ANDA only

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☐ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

Reviewer's Assessment:

b) HOW SUPPLIED section

i) Is the information accurate? ☐ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☐ N/A
If "No," explain.

Reviewer's Assessment:

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

e) For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Reviewer's Assessment:

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets, for oral use

Tablets: 200 mg dasabuvir, 8.33 mg ombitasvir, 50 mg paritaprevir, and 33.33 mg ritonavir (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	yes	Accept
Dosage form, route of administration	yes	Accept
Controlled drug substance symbol (if applicable)	NA	NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	yes	Accept

Conclusion: Acceptable
The trade name Viekira Pak changed to Viekira XR ,
the establish name and dosage form changed to: (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets, for oral use

(b) "Full Prescribing Information" Section

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

VIEKIRA XR is dasabuvir, ombitasvir, paritaprevir, ritonavir fixed dose combination tablets.

1. Revise the statement regarding the content of each tablet to read, "[redacted] (b) (4) 200 mg of dasabuvir equivalent to 216 mg of dasabuvir sodium monohydrate, 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir".

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

Conclusion: Acceptable

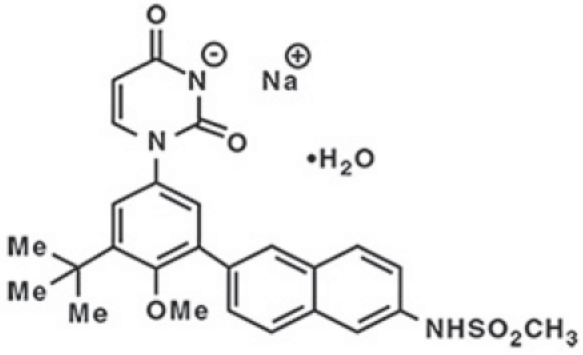
2. Revise the statement regarding the content of each tablet to read, "Each VIEKIRA XR tablet contains 200 mg of dasabuvir equivalent to 216 mg of dasabuvir sodium monohydrate, 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir".

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

VIEKIRA XR fixed dose combination tablet includes a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor (dasabuvir), 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. The tablets are for oral administration.

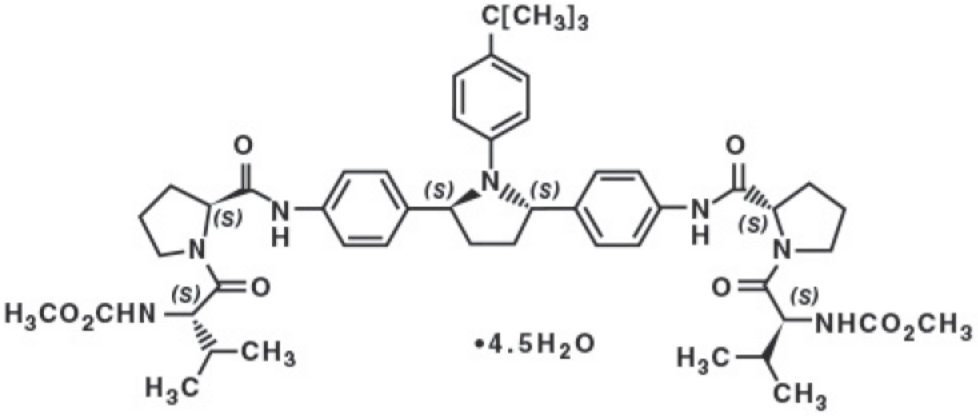
Dasabuvir

The chemical name of dasabuvir is Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1). The molecular formula is $C_{26}H_{26}N_3O_5S•Na•H_2O$ (salt, hydrate) and the molecular weight of the drug substance is 533.57 (salt, hydrate). The drug substance is white to pale yellow to pink powder, slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol. Dasabuvir has the following molecular structure:



Ombitasvir

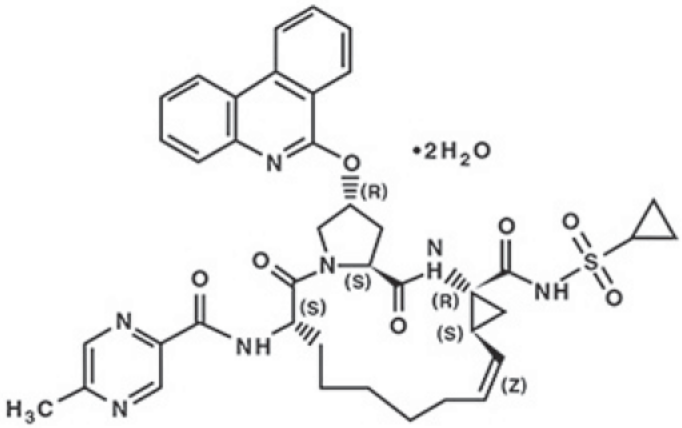
The chemical name of ombitasvir is Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate. The molecular formula is $C_{50}H_{67}N_7O_8•4.5H_2O$ (hydrate) and the molecular 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

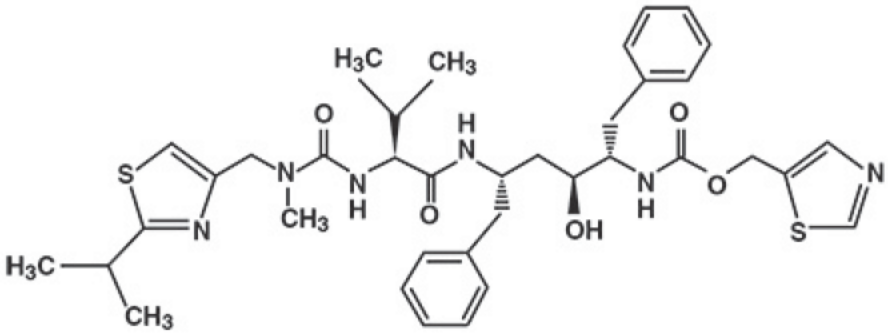
The chemical name of paritaprevir is (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate. The molecular formula is $C_{40}H_{43}N_7O_7S•2H_2O$ (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-methyethyl)-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:



Dasabuvir, Ombitasvir, Paritaprevir, Ritonavir Film-Coated Bilayer Tablets

Dasabuvir, ombitasvir, paritaprevir, and ritonavir film-coated bilayer tablets consist of an extended release (ER) layer and an immediate release (IR) layer. The ER layer contains 200 mg dasabuvir. The ER layer of the tablet also contains copovidone, K value 28, hypromellose 2208, 17,7000 (mPa*s), colloidal silicon dioxide/colloidal anhydrous silica and magnesium stearate. The IR layer contains 8.33 mg ombitasvir, 50 mg paritaprevir and 33.33 mg ritonavir. The IR layer of the tablet also contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, hypromellose 2208, 17,700 mPa*s, magnesium stearate, hypromellose (6 mPa*s), hypromellose (15 mPa*s), polyethylene glycol 400, hydroxypropyl cellulose, polysorbate 80, polyethylene glycol 3350/macrogol 4000, talc, titanium dioxide, and iron oxide yellow.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	yes	accept
Dosage form and route of administration	yes	accept
Active moiety expression of strength with equivalence statement for salt (if applicable)	yes	accept
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	yes	accept
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	yes	accept
Chemical name, structural formula, molecular weight	yes	accept
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	yes	accept

Conclusion: Satisfactory
The drug substance and excipient for the bilayer tablet are separately listed for each layer . Information provided is adequate.

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

VIEKIRA XR 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 three tablets. The NDC number is 0074-0063-28.

Dasabuvir, ombitasvir, paritaprevir, and ritonavir 200 mg/8.33 mg/50 mg/33.33 mg tablets are pale yellow-colored, film-coated, oblong shaped, debossed with "3QD" on one side.

Store at or below 30°C (86°F).

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	yes	accept
Available units (e.g., bottles of 100 tablets)	yes	accept
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	yes	accept
Special handling (e.g., protect from light, do not freeze)	yes	accept
Storage conditions	yes	accept

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	yes	accept

Conclusion: Satisfactory

VIEKIRA XR 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 three tablets. The NDC number is 0074-0063-28.

Dasabuvir, ombitasvir, paritaprevir, and ritonavir 200 mg/8.33 mg/50 mg/33.33 mg tablets are pale yellow-colored, film-coated, oblong shaped, debossed with "3QD" on one side.

Store at or below 30°C (86°F).

2. Container and Carton Labeling

1). Immediate Container Label

(b)(4)

(b)(4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	use Revise to: VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets, (b)(4)	Revise
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	yes	accept
Route of administration 21.CFR 201.100(b)(3))	yes	accept
Net contents* (21 CFR 201.51(a))	yes	accept
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	NA	NA
Lot number per 21 CFR 201.18	yes	accept
Expiration date per 21 CFR 201.17	yes	accept
"Rx only" statement per 21 CFR 201.100(b)(1)	yes	accept
Storage (not required)	yes	accept
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	yes	Acept
Bar Code per 21 CFR 201.25(c)(2)***		
Name of manufacturer/distributor (21 CFR 201.1)		
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: see below

A. All Container Labels, Carton Labeling, and (b)(4)

(b) (4)

B. Container Label (Daily dose wallet pack)

1. The lot number and expiration date are required on the immediate container per 21 CFR 201.10(i) and 21 CFR 201.17, respectively. Add both to the back panel of the packaging.

2. Revise the daily treatment instructions from, (b)(4) to 'Take all 3 tablets once daily at the same time with a meal' to mitigate the risk for errors identified in the Labeling Comprehension Supplementary Round of testing.

Carton Labeling

7 day Carton

(b)(4)

28 day carton

(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))	Revise to: VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets, for oral	Revise
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	NA	NA
Net contents (21 CFR 201.51(a))	yes (28 day carton)	accept
Lot number per 21 CFR 201.18	Yes	
Expiration date per 21 CFR 201.17	Yes	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Yes	
Sterility Information (if applicable)	NA	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	On 7 day carton	accept
Storage Conditions	Yes	accept
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	accept
Bar Code per 21 CFR 201.25(c)(2)**	Yes	accept
Name of manufacturer/distributor	Yes	accept
"See package insert for dosage information" (21 CFR 201.55)	Yes	accept
"Keep out of reach of children" (optional for Rx, required for OTC)	Yes	**accept**
Route of Administration (not	Yes	**accept**

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion:

C. Carton Label (Monthly wallet pack)

1. The net quantity statement does not appear on the Principal Display Panel (PDP). Per Office of Pharmaceutical Quality (OPQ), add the following statement, "This carton contains 84 Tablets packaged as follows: 4 weekly cartons of therapy. Each weekly carton contains 21 tablets in 7 wallets of 3 tablets each.", to the PDP for clarity and ensure it appears away from the product strength statement and with less prominence.

D. Carton Label (Weekly wallet pack)

1. The net quantity statement does not appear on the PDP. Per Office of Pharmaceutical Quality (OPQ), add the following statement, "This carton contains 21 Tablets packaged as follows: 7 wallets for 1 week of treatment. Each wallet contains 3 tablets", on the PDP for clarity and ensure it appears away from the product strength statement and with less prominence.

E. (b)(4)

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Adequate.
Shrikant N. Pagay, Review Completion Date June 20, 2016

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D., June 23, 2016
Branch Chief (Acting), Branch 3, ONDP.

II. List of Deficiencies To Be Communicated

No unsent deficiencies

III. Attachments

A. Lifecycle Knowledge Management

Final Risk Table for Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir Tablets (NDA 208624)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability	Degradants mostly formed during manuf process	8		L	
Physical stability (solid state)	Numbers set by (b)(4) components.	48	Controls on processes, and packaging mitigate risk. Closely-related 206619 product was robust relative to (b)(4) will not be tested in future.	L	(b)(4)
Content uniformity	Drug load (b)(4)	24	(b)(4)	L	
Microbial limits		6		L	
Dissolution IR Layer		32	Formulation design	L	

BCS Class II & IV			(b)(4) revised specification time point		
Dissolution ER Layer		**36**	(b)(4) revised acceptance criteria	L	
Alcohol Dose Dumping ER layer		**64**	Slight dose dumping induced by 40% alcohol in 0.1 N HCl observed; Labeling restrains comsumption of alcohol within 4 hrs of taking the DP	L	
Tablet water content	(b)(4)	**M**	(b)(4)	L	
Drug Product Impurity Control		**M**	Dasabuvir is in a separate layer from the other three actives in this bilayer tablet.	L	
Delamination		**24**		L	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)