CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208341Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208341
Review 2

Drug Name/Dosage Form	Epclusa (Sofosbuvir and Velpatasvir) Tablets
Strength	400mg / 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Presubmission	09-Oct-2015	Presubmission
Original	28-Oct-2015	Original
Amendment	06-Jan-2016	Amendment
Amendment	05-Feb-2016	Amendment
Amendment	23-Mar-2016	Amendment
Amendment	13-Apr-2016	Amendment
Amendment	08-Jun-2016	Labeling
Amendment	15-Jun-2016	Amendment

Quality Review Team

Discipline	Reviewer	Secondary Reviewer
ATL	Stephen Miller	
Drug product	George Lunn	Stephen Miller
Drug Substance	Mouli (Sithamalli) Chandramouli	Kasturi Srinivasachar
Biopharm	Larry(Ge) Bai	Sandra Suarez
Process	Ying Wang	Upinder S. Atwal
Facilities	Christina Capacci-Daniel	Derek Smith
ORA	Paul Perdue, Jr.	
OTR	Yang Yang	Lucinda Buhse
RBPM	Florence Aisida	

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
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	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate	3/17/16	
	III			Adequate	3/17/16	
	III			Adequate	3/17/16	
	III			Adequate	3/17/16	

(b) (4)	III	(b) (4)	Adequate	3/17/16	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 118605		Sofosbuvir & Valpatasvir studies

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

All manufacturing facilities have now been determined to be in acceptable status. From the Product Quality perspective, NDA 208341 is recommended for approval.

Labeling recommendations from the Product Quality perspective have been provided to the OND PM, and were considered during final labeling. All labels and labeling remain acceptable from the Product Quality perspective.

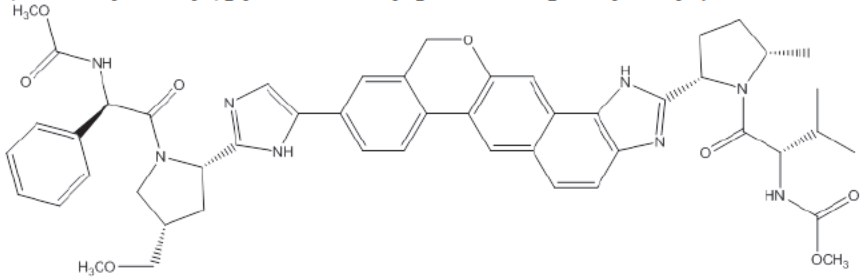
1. Summary of Complete Response issues: NA
2. Action letter language, related to critical issues such as expiration date: We also acknowledge receipt of information related to Epclusa (sofosbuvir and valpatasvir) 400mg/100mg fixed-dose combination tablet for your Gilead Access Program that was reviewed as part of this application.
3. Benefit/Risk Considerations: Evaluation of the quality aspects of Epclusa tablets supports approval without consideration of specific benefit/risk aspects. This is a solid-oral dosage form with conventional packaging and simple dosing recommendations.

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

II. Summary of Quality Assessments

A. Velpatasvir Drug Substance - Quality Summary

1. Chemical Name or IUPAC Name/Structure: Velpatasvir, Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-*d*]imidazol-9-yl}-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate



2. Properties/CQAs Relevant to Drug Product Quality
Velpatasvir is (b) (4). The material is (b) (4) and has no defined melting point. Identity and purity are the CQAs and physical attributes are not important.

3. List of starting materials: [redacted]
4. Suppliers of starting materials (site): Each starting material has been sourced from [redacted] different suppliers and must conform to specification. Each drug substance manufacturing site qualifies the suppliers of the regulatory starting materials using their vendor qualification procedures.
5. Summary of Synthesis: [redacted]
6. Process
   a. Non-sterile [redacted] process. In addition to specifications for starting materials, isolated intermediates and the drug substance, there are [redacted] in-process controls.
   b. Critical equipment: None
7. Container Closure: [redacted]
8. Retest Period & Storage Conditions: [redacted]-month when stored [redacted].

A. Sofosbuvir Drug Substance - Quality Summary

1. USAN: Sofosbuvir, Gilead Code Number: GS-7977
2. The data for this drug substance has been reviewed and found acceptable in the previously approved NDA204671.
3. Retest Period & Storage Conditions: The stability data for sofosbuvir supports a recommended storage condition of [redacted] with a retest period of [redacted] months.

B. Drug Product - Quality Summary

1. Strength: Sofosbuvir 400 mg and velpatasvir 100 mg
2. Description/Commercial Image: Pink (or red for the Access version) diamond-shaped film-coated tablets debossed with GSI on one side and 7916 on the other.
3. Summary of Product Design: The most critical aspect of this product is that [redacted] Stability testing of the [redacted] for up to [redacted] months at [redacted] and under various stress conditions shows no increase in impurities [redacted]. The specification includes tests for appearance, identity (by HPLC retention time and UV), assay ([redacted]% for both actives), degradants, content uniformity (USP <905>), dissolution, and microbial limits and is acceptable. The analytical methods are described in reasonable detail and have been validated. Satisfactory batch analyses are provided for 16 batches. Twelve months of data obtained at 25°C/60% RH and 30°C/75% RH and 6 months of data obtained at 40°C/75% RH are provided for 3 batches of more than

(b) (4)% of the planned commercial scale. Supporting stability data are provided for 9 other batches. There are no out of specification results and no trends are observed. No changes were observed in the light cabinet. There is no routine testing for (b) (4) but a limited drug product stress test showed (b) (4) even under stress conditions. Stability studies have been carried out where (b) (4) is used to make batches of tablets. The stability behavior of such batches is no different from batches made using (b) (4). Eventually an end to end study using (b) (4) will be conducted to qualify a (b) (4) month shelf life for the (b) (4)

4. List of Excipients: copovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose. The film coats contain iron oxide red,((b) (4) in Access tablet only), polyethylene glycol (b) (4) polyvinyl alcohol, talc, and titanium dioxide.
5. Process Selection (Unit Operations Summary)
   a. (b) (4)
   b. Proven acceptable range (PAR) and target value for various process parameters are provided in the submission based on DOE and other studies.
   c. Hold times have adequate support, including on-going studies (as amended) for the (b) (4). In-process controls are acceptable and typical for this dosage form. (b) (4) is proposed and adequately supported by studies.
   d. Critical equipment: (b) (4).
6. Container Closure: The tablets are packaged 28 count in 75 mL HDPE bottles containing a polyester (b) (4) coil. The bottles are closed with induction seals and child-resistant closures.
7. Expiration Date & Storage Conditions: The expiration dating period is 24 months with the storage statement of "Store below 30°C". The expiration dating period begins when (b) (4).
8. List of co-packaged components: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Epclusa
Non Proprietary Name of the Drug Product	Sofosbuvir and Velpatasvir
Non Proprietary Name of the Drug Substance	Sofosbuvir and Velpatasvir
Proposed Indication(s) including Intended Patient Population	Treatment of chronic infection with the Hepatitis C virus
Duration of Treatment	12 weeks
Maximum Daily Dose	1 tablet/day (400 mg of sofosbuvir and 100 mg of velpatasvir per day)

Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: SOF (Class III); VEL (Class IV)
   - Drug Product: With the proposed dissolution method, the drug product dissolves relatively fast but it cannot be categorized to rapidly dissolving or very rapidly dissolving drug product since one of the two APIs belongs to BCS Class IV. Current dissolution acceptance criterion is Q = (b)(4)% at 20 minutes for both SOF and VEL.

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: N/A
   - IVIVC: N/A

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations

None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:
The recommendation from the Product Quality perspective for this NDA is for Approval.

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: 2016.06.23 14:55:45 -04'00'

Stephen Miller, Ph.D. June 23, 2016
QAL/CMC-Lead; Branch-III; ONDP; OPQ

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ASSESSMENT OF THE BIOPHARMACEUTICS

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

The drug product Sofosbuvir/Velpatasvir Fixed-Dose Combination Tablet (400 mg/100 mg) is developed to provide treatment to chronic hepatitis C virus (HCV) infection in adults. The drug product contains two drug substances: Sofosbuvir (SOF) and Velpatasvir (VEL). The SOF belongs to BCS Class III in crystalline form (b) (4) and has high solubility (Table 1). The VEL belongs to BCS Class IV and it is (b) (4) free base. Table 2 shows the solubility of the VEL. (b) (4)

The drug product is formulated as film-coated tablet with immediate release of both active ingredients.

Table 1. SOF solubility at 37 °C

pH (Media)	Solubility (mg/mL)
1.2[1] (HCl)	1.3
2.0 (HCl)	2.0
4.5 (Acetate Buffer)	2.1
6.8 (Phosphate Buffer)	3.6
5.0 (FeSSIF)	1.8
6.5 (FaSSIF)	2.1

Table 2. VEL solubility at 37 °C, (b) (4)

pH (Media)	Solubility (mg/mL)
1.2 (HCl)	> 36
2 (HCl)	4.1
4.5 (Acetate Buffer)	< 0.1
5.0 (Acetate Buffer)	< 0.1
6.8 (Phosphate Buffer)	< 0.1
5.0 (FeSSIF)	0.3
6.5 (FaSSIF)	< 0.1

Dissolution Method

The proposed dissolution method is summarized in Table 3.

Table 3. Proposed dissolution method

Parameter	Setting
Apparatus	USP Dissolution Apparatus 2 (paddle method)
Volume	900 mL
Paddle Speed	75 rpm
Medium pH	5.0
Buffer and Concentration	50 mM sodium acetate
Surfactant and Concentration	0.5% w/v cetyl trimethylammonium bromide (CTAB)

Dissolution Method Development

(b) (4)

(b) (4)

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clinical studies (e.g. 14SXG001UR, 14SXG002UR and 14SXG003UR). There are no batches presented by the Applicant showing different in vivo performance and tested in vitro by the proposed dissolution method. It is not feasible to establish the biopredictive power of the proposed dissolution method.

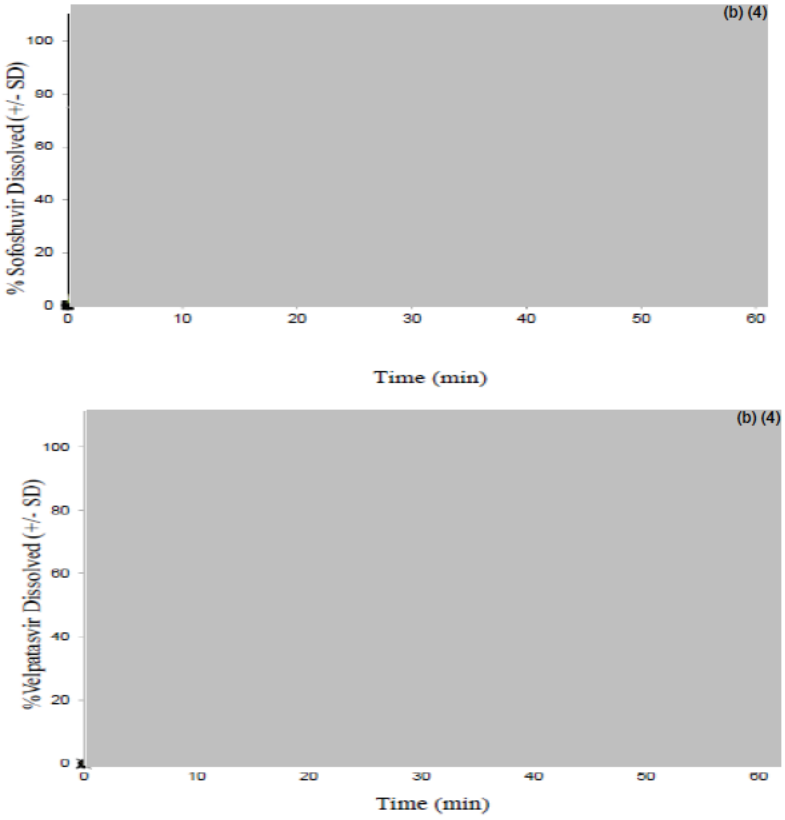
Reviewer's Assessment: The Applicant claimed that the dissolutions of both drug substances are limited by the (b) (4) . This is reasonable because the DP is formulated as immediate release drug and both APIs have high solubility in the proposed dissolution medium. The Applicant provided data demonstrating that the proposed dissolution method has discriminating capability against these two factors. The Applicant also conducted studies on the impact of variations of some of the CPPs and CMAs on dissolution. Results show the proposed dissolution method does not have discriminating capability against the studied CPPs in the PARs and CMAs including (b) (4) Lacking of discriminating capability against the above parameters is not critical issue for the proposed dissolution method since the manufacturing process will be operated within PARs. In addition, the proposed in-process testing ensures the quality of (b) (4) . There is no available data to establish the biopredictive power of the proposed dissolution method. It is noted that the dissolution method discriminates for batches manufactured at (b) (4) .

Dissolution Acceptance Criterion

The originally proposed dissolution criterion for both components was NLT (b) (4)% (Q) dissolved at 20 minutes. Figure 10 shows the dissolution profiles from 13 clinical and clinical stability batches. Obviously, the originally proposed dissolution acceptance criterion is too permissive as at 20 minutes, both dissolved PAIs are close to (b) (4)%. During the review cycle, the Applicant was asked to tighten the dissolution acceptance criterion based on the available relevant data. The Applicant agreed to tighten the acceptance criterion to Q= (b) (4)% at 20 minutes. According to the Applicant, this newly proposed dissolution acceptance criterion would pass batch 14SXG001UR while maintaining appropriate discriminatory capability for routine quality control testing of SOF/VEL tablets. Batch 14SXG001UR was used in pivotal Phase 3 clinical studies for efficacy but as shown in Figure 10, it has (b) (4) compared to the other clinical batches. The Applicant was asked to explain how the manufacturing conditions of (b) (4) of batch 14SXG001UR as claimed resulted in its (b) (4). According to the Applicant

(response to IR received on 01/06/2016), the phenomena could be reproduced in the development investigational study. However, the exact mechanism remained unclear. According to the Applicant, this particular batch did not behave differently in vivo. Its dissolution profile sets the lowest dissolution limit for the future batches. As mentioned by the process reviewer, Ying Wang above, Applicant's studies results demonstrated that within intended commercial production rate range ((b) (4) tablets per minute) the tablet dissolution rates are similar and all meet the specification regardless of the (b) (4) . Batch 14SXG001UR was (b) (4) . Thus, the proposed range of production rate of the commercial manufacturing process excludes the possibility of seeing batch similar to batch 14SXG001UR, which has (b) (4) .

Figure 10. Sofosbuvir and Velpatasvir dissolution profiles from SOF/VEL clinical and clinical stability batches



Reviewer's Assessment: As mentioned above, the biopharmaceutics review team recommended an acceptance criterion that rejects a batch (Lot 14SXG001UR) with (b) (4) . Although this batch was tested in clinical trials, the dissolution profile is (b) (4) than the other two clinical trial batches (14SXG002UR and 14SXG003UR, Fig 10). Thus, the impact of potentially (b) (4) on the efficacy of the drug product resulting from (b) (4) profile of some batches was discussed with the Clinical pharmacology review team via email. It was

communicated to the clinical pharmacology review team that since there is (b) (4) .

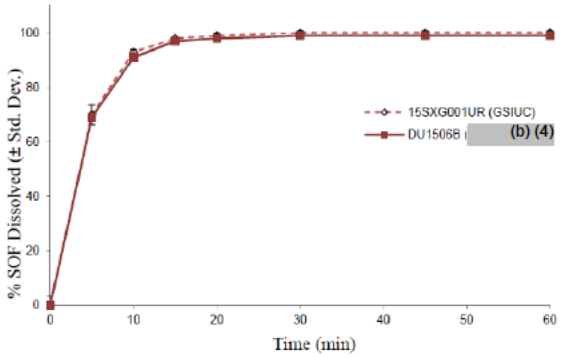
Based on the comments from Dr. Shirley Seo on 02/26/2016, Cmax is not a contributor in the overall efficacy for this kind of drug. Thus, (b) (4) of batch 14SXG001UR should not cause any efficacy issue. The tightened dissolution acceptance criterion of Q= (b) (4) % at 20 minutes proposed by the Applicant is reasonable based on all available data.

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

The proposed commercial formulation is the same as that used in the clinical studies. Clinical manufacturing and commercial manufacturing have similar processes.

There are two proposed commercial manufacturing sites: GSIUC and (b) (4). The same manufacturing process will be applied at both sites. Dissolution data from representative drug product lots 15SXG001UR and DU1506B manufactured at GSIUC and at (b) (4), respectively are shown in **Figure 11** and the *f2* analyses are summarized in **Table 6** and **Table 7**. Data demonstrate that the two proposed commercial manufacturing sites have similar drug products.

Figure 11. Sofosbuvir and Velpatasvir Dissolution Profiles from SOF/VEL Tablets Lot 15SXG001UR (GSIUC) and Lot DU1506B ((b) (4))



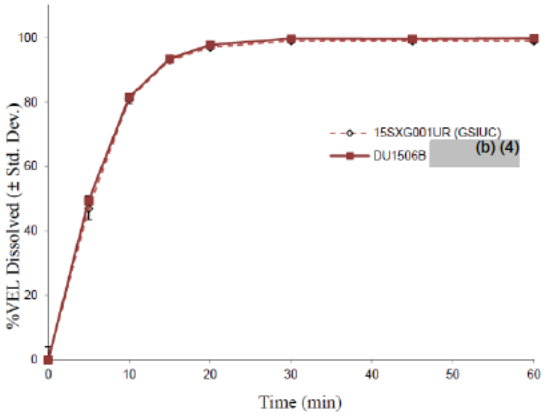


Table 6. Sofosbuvir Dissolution Data Used in *f2* Analysis for Tablets from Each Manufacturing Site

Lot	15SXG001UR (GSIUC)	DU1506B (b) (4)
Time (min)	Percent SOF Dissolved	
5	70	69
10	93	91
15	98	97
f2	88	

Table 7. Sofosbuvir Dissolution Data Used in f2 Analysis for Tablets from Each Manufacturing Site

Lot	15SXG001UR (GSIUC)	DU1506B (b) (4)
Time (min)	Percent VEL Dissolved	
5	47	50
10	81	81
15	93	93
f2	85	

Reviewer's Assessment: The two proposed commercial DP manufacturing sites are adequately bridged with provided dissolution data and *f2* analyses.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature: ADEQUATE.

The Applicant conducted a comprehensive dissolution method development to identify the appropriate dissolution apparatus, dissolution medium and volume, surfactant type and concentration, paddle rotation speed, (b) (4) etc. The Applicant tightened the originally proposed dissolution acceptance criterion. The newly proposed dissolution acceptance criterion is supported by the dissolution data of batches tested in pivotal phase 3 clinical trials. Based on our discussion with the process reviewer, the risk in manufacturing batches with (b) (4) has been mitigated by the implementation of appropriate controls. The dissolution specifications shown in the table below are deemed acceptable.

Apparatus	USP Dissolution Apparatus 2 (Paddle Method)
Stirring Speed	75 rpm
Medium	50 nM sodium acetate at pH 5.0 with 0.5% w/v CTAB
Medium Volume	900 mL
Sampling Times	5, 10, 20, 30 and 45 minutes
Acceptance Criteria	Q = (b) (4)% at 20 minutes for both SOF and VEL

The drug product is formulated as immediate release tablet with high solubility of the two APIs in the proposed dissolution medium. The proposed dissolution method has discriminating ability against the (b) (4) are the two factors that have direct impact on the (b) (4). The method does not have discriminating ability against some CPPs (within PARs) and CMAs such as (b) (4) Lacking of discriminating capability against the above parameters is not critical issue for the proposed dissolution method since the manufacturing process will be operated within PARs. In addition, the proposed in-process testing ensures the quality of (b) (4). It is worth mentioning that the dissolution method discriminates for batches manufactured at the (b) (4)

(b) (4)

There are no formulation and process changes for the to-be-market drug product. Data provided demonstrated the similarity of the two proposed commercial drug product manufacturing sites.

NDA 208341 (Sofosbuvir/Velpatasvir Fixed-Dose Combination Tablet (400 mg/100 mg)) is RECOMMENDED FOR APPROVAL from a Biopharmaceutics perspective.

Ge Bai, Ph.D., 02/29/2016
Biopharmaceutics Reviewer
Office of New Drug Product
Division of Biopharmaceutics

Secondary Review Comments and Concurrence:

I concur with the primary reviewer's assessment of the biopharmaceutics section.
Sandra Suarez Sharp, Ph.D., 03/02/2016
Biopharmaceutics Reviewer
Office of New Drug Product
Division of Biopharmaceutics

ASSESSMENT OF MICROBIOLOGY

To assure drug product safety and confirm no microbial contamination during drug product manufacturing, microbial examination will be conducted. Testing will be performed at release and at the beginning and end of shelf-life for the first three commercial and annual commitment lots of drug product (Section 3.2.P.8.2). The acceptance criteria established according to harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 will be applied.

Reviewer's Assessment: Adequate

The proposed microbial test is adequate for solid oral dosage form.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommended for approval from microbiology perspective

Ying Wang, Ph.D.
2/17/2016

Secondary Review Comments and Concurrence:

I concur.

Upinder Atwal, Ph.D.
Acting Branch Chief
DPA I/Branch III

02/25/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant requests a categorical exclusion from the requirements to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the expected introduction concentration of sofosbuvir and velpatasvir at the point of entry into the aquatic environment, (b) (4) ppb and (b) (4) ppb, respectively, is less than 1 part per billion. The sofosbuvir value takes into account the other sofosbuvir-containing formulations, Sovaldi and Harvoni. To the applicant's knowledge no extraordinary circumstances exist.

Reviewer's Assessment: Adequate. The claim is reasonable and should be accepted. In an e-mail of 3/4/16 James Laurenson, ONDP concurs. There are no hormonal effects in mammalian species, even at very high doses relative to the EICs.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The claim for a categorical exclusion from the requirement to perform an Environmental Assessment is reasonable and should be accepted. There are no hormonal effects in mammalian species, even at very high doses relative to the EICs. In an e-mail of 3/4/16 James Laurenson, ONDP concurs.

George Lunn, Ph.D. Apr 1, 2016
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. Apr 1, 2016
QAL/CMC-Lead; Branch-III; ONDP; OPQ

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

Labeling & Package Insert

1. Package Insert

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

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 400 mg sofosbuvir and 100 mg velpatasvir

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Epclusa™ (sofosbuvir and velpatasvir) tablets, for oral use	Adequate
Dosage form, route of administration	Tablets, oral	Adequate
Controlled drug substance symbol (if applicable)	NA	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 400 mg sofosbuvir and 100 mg velpatasvir	Adequate

Conclusion: Adequate.

(b) "Full Prescribing Information" Section

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

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	400 mg sofosbuvir and 100 mg velpatasvir	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side	Adequate

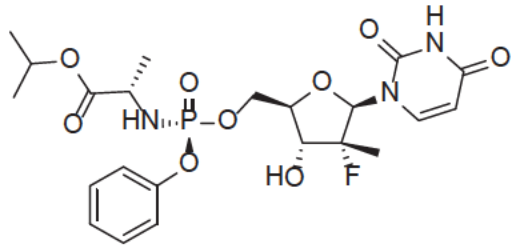
Conclusion: Adequate

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

Epclusa is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase and velpatasvir is an NS5A inhibitor.

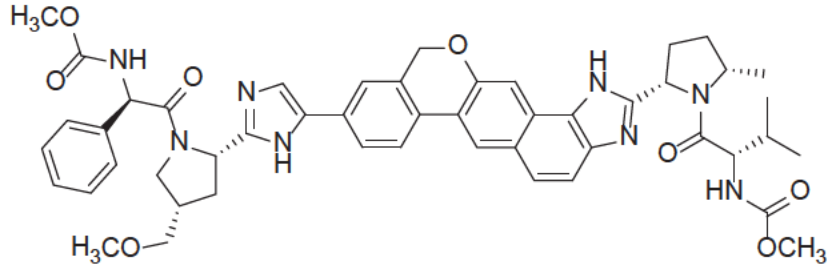
Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir. The tablets include the following inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Sofosbuvir: The IUPAC name for sofosbuvir is (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



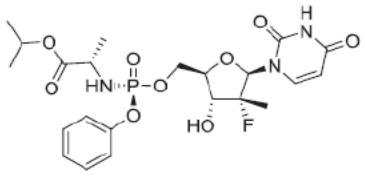
Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37°C and is slightly soluble in water.

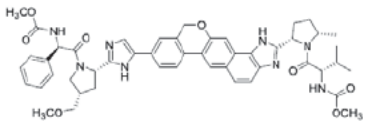
Velpatasvir: The IUPAC name for velpatasvir is Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-*d*]imidazol-9-yl}-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0. It has the following structural formula:



Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.

Item	Information Provided in NDA	Reviewer's Assessment

Proprietary name and established name	Epclusa™ (sofosbuvir and velpatasvir) tablets, for oral use	Adequate
Dosage form and route of administration	Tablets, oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	NA	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	The tablets include the following inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.	Adequate
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase and velpatasvir is an NS5A inhibitor.	Adequate
Chemical name, structural formula, molecular weight	Sofosbuvir: The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular weight of 529.45. It has the following structural formula:  Velpatasvir: The IUPAC name for velpatasvir is Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-	Adequate

	(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular weight of 883.0. It has the following structural formula: 	
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37oC and is slightly soluble in water. Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.	Adequate

Conclusion: Adequate

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

Each EPCLUSA tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir, is pink, diamond-shaped, film-coated, debossed with "GSI" on one side and "7916" on the other. Each bottle contains 28 tablets (NDC 61958-2201-1), polyester coil, and is closed with a child resistant closure.

Store below 30 ˚C (86 ºF). Dispense only in original container.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir.	Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 28 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side	Adequate
Special handling (e.g., protect from light, do not freeze)	Dispense only in original container	Adequate
Storage conditions	Store below 30 ˚C (86 ºF)	Adequate

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)	Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404	Adequate

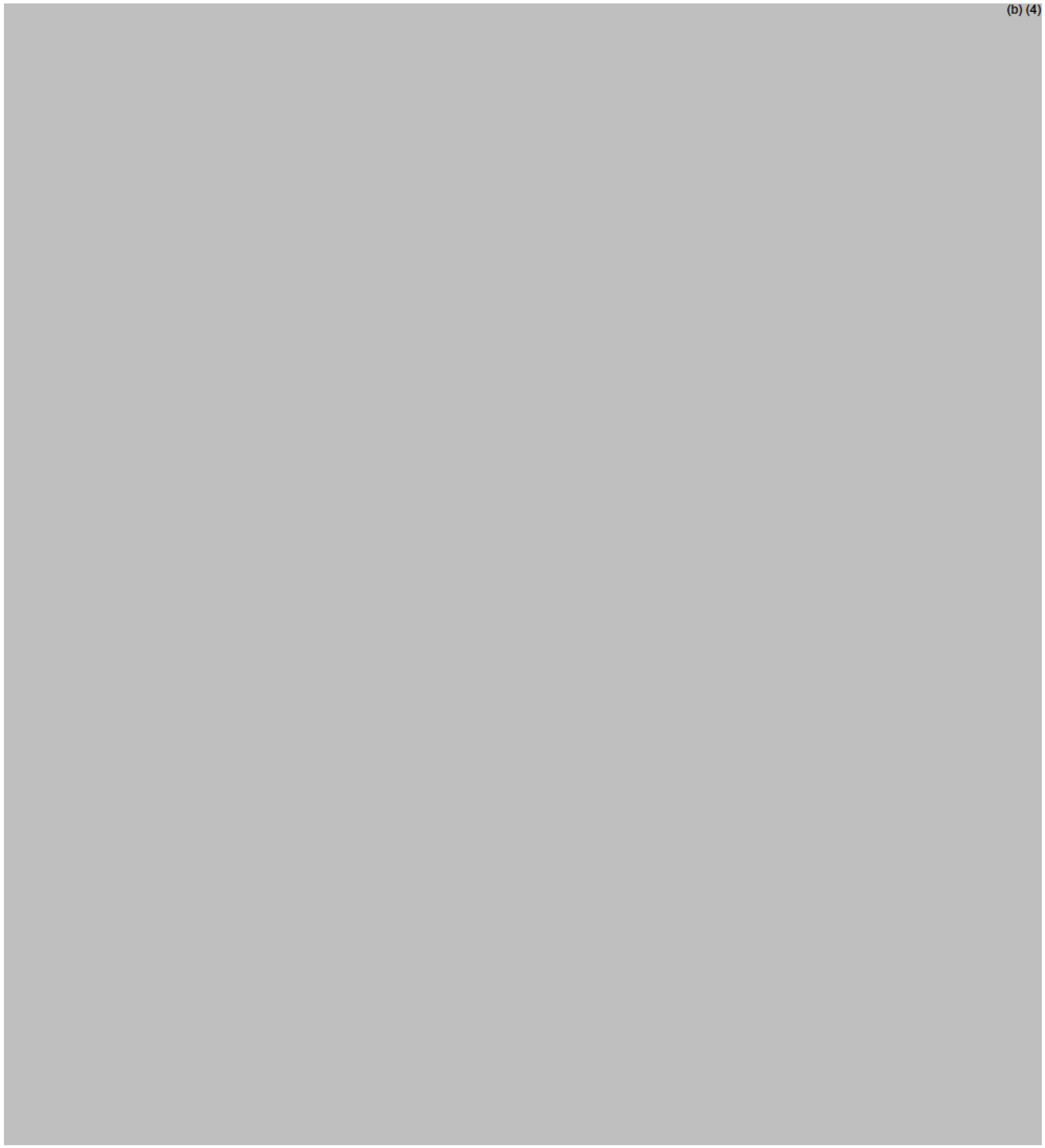
Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

The US container label is as follows.

(b) (4)



The Access container label is as follows.

(b) (4)

Reviewer's Assessment: Adequate.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Epclusa	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Sofosbuvir, velpatasvir tablets 400 mg / 100 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral. Not on container label	Adequate
Net contents* (21 CFR 201.51(a))	28 tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not on container label. This is acceptable**	Adequate
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate
Storage (not required)	Store below 30°C (86°F) (see insert)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 61958-2201-1	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404	Adequate
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

Conclusion: Adequate

2) Carton Labeling
(Carton is for the Access product only; main panels shown).

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))	Epclusa	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Sofosbuvir, velpatasvir tablets 400 mg / 100 mg	Adequate
Net contents (21 CFR 201.51(a))	28 tablets	Adequate
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	NA	
Sterility Information (if applicable)	NA	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	Adequate
Storage Conditions	Store below 30°C (86°F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	61958-XXXX-X	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present	Adequate
Name of manufacturer/distributor	Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404. Manufactured by: (b) (4)	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Present	Adequate
(b) (4)		Adequate

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	NA	

Conclusion: Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
The labeling is acceptable from the Product Quality Perspective.

George Lunn, Ph.D. June 20, 2016
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. June 20, 2016
QAL/CMC-Lead; Branch-III; ONDP; OPQ

II. List of Deficiencies To Be Communicated

No remaining deficiencies.

III. Attachments

A. Lifecycle Knowledge Management

Final Risk Table for Sofosbuvir and Velpatasvir Tablets

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		L		L	(b) (4)
Physical stability (solid state)		M	Supporting data show API form is inherently stable and shows (b) (4)	L	
Content uniformity	(b) (4)	L		L	
Microbial limits		L		L	
Dissolution – BCS Class III & IV	• (b) (4) • Permissive dissolution acceptance criteria	M	• (b) (4) • Evaluation and comparison of dissolution profiles of clinical and clinical stability batches • Evaluation and recommendation of dissolution acceptance criteria	L	One API (SOF) has high solubility. The other API (VEL) has low solubility (b) (4). The drug product is formulated as immediate release tablet. (b) (4) The proposed dissolution method has discriminating ability against the (b) (4) The recommended stringent dissolution acceptance criteria will ensure the quality of the drug product. Overall, the risk of dissolution remains low after review of dissolution method and dissolution data.
(b) (4)		M	(b) (4)	L	
Drug Product Impurity Control		L		L	
Risk Factors associated with Patient Use	Moderately-sized tablet (10mm x 20 mm); no score or dispersing instructions	L		L	

Recommendation: Pending

NDA 208341
Review 1

Drug Name/Dosage Form	Sofosbuvir and Velpatasvir
Strength	400mg / 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Presubmission	09-Oct-2015	Presubmission
Original	28-Oct-2015	Original
Amendment	06-Jan-2016	Amendment
Amendment	05-Feb-2016	Amendment
Amendment	23-Mar-2016	Amendment

Quality Review Team

Discipline	Reviewer	Secondary Reviewer
ATL	Stephen Miller	Bala Shanmugam
Drug product	George Lunn	Stephen Miller
Drug Substance	Mouli (Sithamalli) Chandramouli	Kasturi Srinivasachar
Biopharm	Larry(Ge) Bai	Suarez, Sandra
Process	Ying Wang	Atwal, Upinder S
Facilities	Christina Capacci-Daniel	Smith, Derek
ORA	Perdue Jr Paul	Perdue Jr Paul
OTR	Yang, Yang	Buhse, Lucinda
RBPM	Florence Aisida	

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate.	3/17/16	
	III			Adequate	3/17/16	
	III			Adequate	3/17/16	
	III			Adequate	3/17/16	

(b) (4)	III		(b) (4)	Adequate	3/17/16
	III			Adequate	3/17/16

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this time, evaluation of all manufacturing facilities is not yet complete. Additionally, the acceptance criteria for velpatasvir impurities in the drug substance and drug product specifications are under discussion with the applicant. For these reasons, the recommendation from the Product Quality perspective is PENDING at this time.

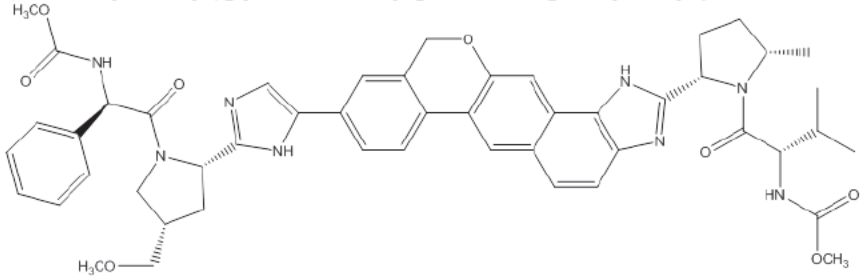
1. Summary of Complete Response issues: NA at this time
2. Action letter language, related to critical issues such as expiration date: NA at this time
3. Benefit/Risk Considerations: NA at this time

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

II. Summary of Quality Assessments

A. Velpatasvir Drug Substance - Quality Summary

1. Chemical Name or IUPAC Name/Structure: Velpatasvir, Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-*d*]imidazol-9-yl}-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate



2. Properties/CQAs Relevant to Drug Product Quality
   Velpatasvir is a [redacted (b) (4)]. The material is [redacted (b) (4)] and has no defined melting point. Identity and purity are the CQAs and physical attributes are not important.
3. List of starting materials: [redacted (b) (4)]
4. Suppliers of starting materials (site): Each starting material has been sourced from [redacted (b) (4)] different suppliers and must conform to specification. Each drug substance manufacturing site qualifies the suppliers of the regulatory starting materials using their vendor qualification procedures.
5. Summary of Synthesis: [redacted (b) (4)]

(b) (4)

6. Process
   a. Non-sterile (b) (4) process. In addition to specifications for starting materials, isolated intermediates and the drug substance, there are (b) (4) in-process controls.
   b. Critical equipment: None
7. Container Closure: (b) (4)
8. Retest Period & Storage Conditions: (b) (4)-month when stored (b) (4).

A. Sofosbuvir Drug Substance - Quality Summary

1. USAN: Sofosbuvir, Gilead Code Number: GS-7977
2. The data for this drug substance has been reviewed and found acceptable in the previously approved NDA204671.
3. Retest Period & Storage Conditions: The stability data for sofosbuvir supports a recommended storage condition of (b) (4) with a retest period of (b) (4) months.

B. Drug Product - Quality Summary

1. Strength: Sofosbuvir 400 mg and velpatasvir 100 mg
2. Description/Commercial Image: Pink (or red for the Access version) diamond-shaped film-coated tablets debossed with GSI on one side and 7916 on the other.
3. Summary of Product Design: The most critical aspect of this product is that (b) (4) Stability testing of the (b) (4) for up to (b) (4) months at (b) (4) and under various stress conditions shows no increase in impurities (b) (4). The specification includes tests for appearance, identity (by HPLC retention time and UV), assay ((b) (4)% for both actives), degradants, content uniformity (USP <905>), dissolution, and microbial limits and is acceptable. The analytical methods are described in reasonable detail and have been validated. Satisfactory batch analyses are provided for 16 batches. Twelve months of data obtained at 25°C/60% RH and 30°C/75% RH and 6 months of data obtained at 40°C/75% RH are provided for 3 batches of more than 10% of the planned commercial scale. Supporting stability data are provided for 9 other batches. There are no out of specification results and no trends are observed. No changes were observed in the light cabinet. There is no routine testing for (b) (4) but a limited drug product stress test showed (b) (4). Stability studies have been carried out where (b) (4) is used to make batches of tablets. The stability behavior of such batches is no different from batches made using (b) (4). Eventually an end to end study

using [redacted] will be conducted to qualify a [redacted] month shelf life for the [redacted]

4. List of Excipients: copovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose. The film coats contain iron oxide red,([redacted] in Access tablet only), polyethylene glycol [redacted] polyvinyl alcohol, talc, and titanium dioxide.
5. Process Selection (Unit Operations Summary)
   a. [redacted]
   b. Proven acceptable range (PAR) and target value for various process parameters are provided in the submission based on DOE and other studies.
   c. Hold times have adequate support, including on-going studies (as amended) for the [redacted] In-process controls are acceptable and typical for this dosage form. [redacted] is proposed and adequately supported by studies.
   d. Critical equipment: [redacted]
6. Container Closure: The tablets are packaged 28 count in 75 mL HDPE bottles containing a polyester [redacted] coil. The bottles are closed with induction seals and child-resistant closures.
7. Expiration Date & Storage Conditions: The expiration dating period is 24 months with the storage statement of "Store below 30°C". The expiration dating period begins when [redacted].
8. List of co-packaged components: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Epclusa
Non Proprietary Name of the Drug Product	Sofosbuvir and Velpatasvir
Non Proprietary Name of the Drug Substance	Sofosbuvir and Velpatasvir
Proposed Indication(s) including Intended Patient Population	Treatment of chronic infection with the Hepatitis C virus
Duration of Treatment	12 weeks
Maximum Daily Dose	1 tablet/day (400 mg of sofosbuvir and 100 mg of velpatasvir per day)
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: SOF (Class III); VEL (Class IV)
   - Drug Product: With the proposed dissolution method, the drug product dissolves relatively fast but it cannot be categorized to rapidly dissolving

or very rapidly dissolving drug product since one of the two APIs belongs to BCS Class IV. Current dissolution acceptance criterion is Q = (b)(4)% at 20 minutes for both SOF and VEL.

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: N/A
   - IVIVC: N/A

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations

We have the following recommendations for consideration at an appropriate time in labeling negotiations:

- Submit revised container labels with "Trademark" replaced with Epclusa
- In Section 11, list the inactive ingredients in alphabetical order

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:
The recommendation from the Product Quality perspective for this NDA is PENDING at this time.

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: 2016.04.01 15:21:02 -04'00'

Stephen Miller, Ph.D. Apr 1, 2016
QAL/CMC-Lead; Branch-III; ONDP; OPQ

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

This assessment is still in progress. The Facility Recommendation is **PENDING** at this time.

Christina Capacci-Daniel, PhD – 3/31/2016
Consumer Safety Officer / Acting QAL – OPQ/OPF/DIA/IABII

Secondary Review Comments and Concurrence:

Review In Progress Awaiting EIRs

Derek S. Smith, Ph.D. – 3/31/2016

ASSESSMENT OF THE BIOPHARMACEUTICS

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

The drug product Sofosbuvir/Velpatasvir Fixed-Dose Combination Tablet (400 mg/100 mg) is developed to provide treatment to chronic hepatitis C virus (HCV) infection in adults. The drug product contains two drug substances: Sofosbuvir (SOF) and Velpatasvir (VEL). The SOF belongs to BCS Class III in crystalline form (b) (4) and has high solubility (Table 1). The VEL belongs to BCS Class IV and it is (b) (4) free base. Table 2 shows the solubility of the VEL. (b) (4)

The drug product is formulated as film-coated tablet with immediate release of both active ingredients.

Table 1. SOF solubility at 37 °C

pH (Media)	Solubility (mg/mL)
1.2[1] (HCl)	1.3
2.0 (HCl)	2.0
4.5 (Acetate Buffer)	2.1
6.8 (Phosphate Buffer)	3.6
5.0 (FeSSIF)	1.8
6.5 (FaSSIF)	2.1

Table 2. VEL solubility at 37 °C, (b) (4)

pH (Media)	Solubility (mg/mL)
1.2 (HCl)	> 36
2 (HCl)	4.1
4.5 (Acetate Buffer)	< 0.1
5.0 (Acetate Buffer)	< 0.1
6.8 (Phosphate Buffer)	< 0.1
5.0 (FeSSIF)	0.3
6.5 (FaSSIF)	< 0.1

Dissolution Method

The proposed dissolution method is summarized in Table 3.

Table 3. Proposed dissolution method

Parameter	Setting
Apparatus	USP Dissolution Apparatus 2 (paddle method)
Volume	900 mL
Paddle Speed	75 rpm
Medium pH	5.0
Buffer and Concentration	50 mM sodium acetate
Surfactant and Concentration	0.5% w/v cetyl trimethylammonium bromide (CTAB)

Dissolution Method Development

(b) (4)

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The Applicant used Batch DU1301B in phase 1 clinical studies for bioavailability of the DP. DU1301B has the exactly same formulation as those batches used in pivotal phase 3 clinical studies (e.g. 14SXG001UR, 14SXG002UR and 14SXG003UR). There are no batches presented by the Applicant showing different in vivo performance and tested in vitro by the proposed dissolution method. It is not feasible to establish the biopredictive power of the proposed dissolution method.

Reviewer's Assessment: The Applicant claimed that the dissolutions of both drug substances are limited by the (b) (4)

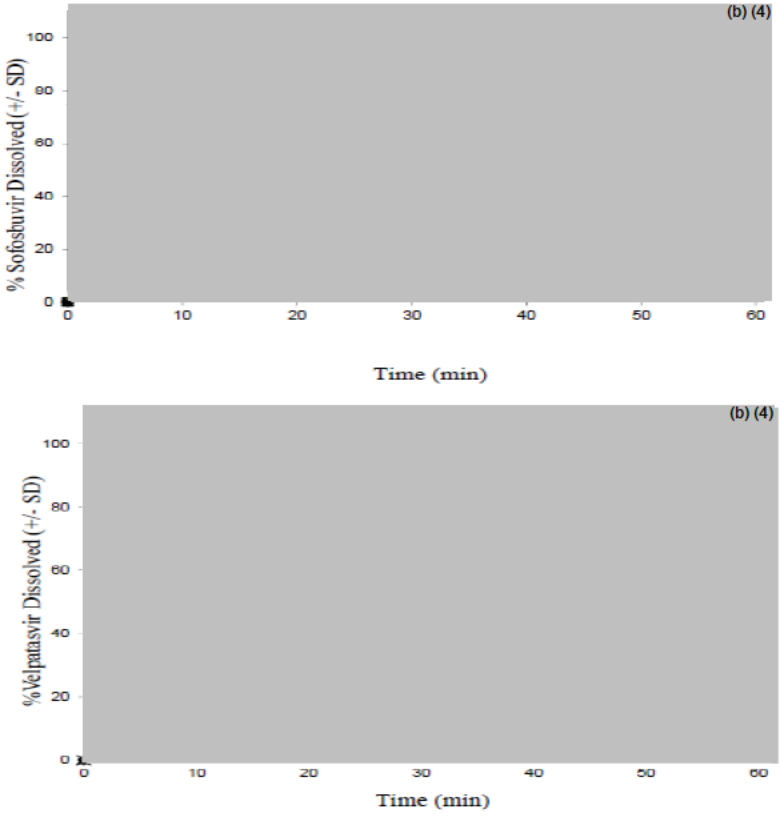
This is reasonable because the DP is formulated as immediate release drug and both APIs have high solubility in the proposed dissolution medium. The Applicant provided data demonstrating that the proposed dissolution method has discriminating capability against these two factors. The Applicant also conducted studies on the impact of variations of some of the CPPs and CMAs on dissolution. Results show the proposed dissolution method does not have discriminating capability against the studied CPPs in the PARs and CMAs including (b) (4) Lacking of discriminating capability against the above parameters is not critical issue for the proposed dissolution method since the manufacturing process will be operated within PARs. In addition, the proposed in-process testing ensures the quality of (b) (4). There is no available data to establish the biopredictive power of the proposed dissolution method. It is noted that the dissolution method discriminates for batches manufactured at the (b) (4)

Dissolution Acceptance Criterion

The originally proposed dissolution criterion for both components was NLT (b) (4)% (Q) dissolved at 20 minutes. Figure 10 shows the dissolution profiles from 13 clinical and clinical stability batches. Obviously, the originally proposed dissolution acceptance criterion is too permissive as at 20 minutes, both dissolved PAIs are close to (b) (4)%. During the review cycle, the Applicant was asked to tighten the dissolution acceptance criterion based on the available relevant data. The Applicant agreed to tighten the acceptance criterion to Q= (b) (4)% at 20 minutes. According to the Applicant, this newly proposed dissolution acceptance criterion would pass batch 14SXG001UR while maintaining appropriate discriminatory capability for routine quality control testing of SOF/VEL tablets. Batch

14SXG001UR was used in pivotal Phase 3 clinical studies for efficacy but as shown in **Figure 10**, it has (b) (4) compared to the other clinical batches. The Applicant was asked to explain how the manufacturing conditions of (b) (4) of batch 14SXG001UR as claimed resulted in its (b) (4). According to the Applicant (response to IR received on 01/06/2016), the phenomena could be reproduced in the development investigational study. However, the exact mechanism remained unclear. According to the Applicant, this particular batch did not behave differently in vivo. Its dissolution profile sets the lowest dissolution limit for the future batches. As mentioned by the process reviewer, Ying Wang above, Applicant's studies results demonstrated that within intended commercial production rate range ((b) (4) tablets per minute) the tablet dissolution rates are similar and all meet the specification regardless of the (b) (4). Batch 14SXG001UR was (b) (4). Thus, the proposed range of production rate of the commercial manufacturing process excludes the possibility of seeing batch similar to batch 14SXG001UR, which has (b) (4).

Figure 10. Sofosbuvir and Velpatasvir dissolution profiles from SOF/VEL clinical and clinical stability batches



Reviewer's Assessment: As mentioned above, the biopharmaceutics review team recommended an acceptance criterion that rejects a batch (Lot 14SXG001UR) with (b) (4). Although this batch was tested in clinical trials, the dissolution profile is (b) (4) than the other two clinical trial batches (14SXG002UR and 14SXG003UR, Fig 10). Thus, the impact of potentially (b) (4) on the efficacy of the drug product resulting from (b) (4) profile of some batches was discussed with the Clinical pharmacology review team via email. It was communicated to the clinical pharmacology review team that since there is (b) (4)

Based on the comments from Dr. Shirley Seo on 02/26/2016, Cmax is not a contributor in the overall efficacy for this kind of drug. Thus, (b) (4) of batch 14SXG001UR should not cause any efficacy issue. The tightened dissolution acceptance criterion of Q= (b) (4)% at 20 minutes proposed by the Applicant is reasonable based on all available data.

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

The proposed commercial formulation is the same as that used in the clinical studies. Clinical manufacturing and commercial manufacturing have similar processes.

There are two proposed commercial manufacturing sites: GSIUC and (b) (4). The same manufacturing process will be applied at both sites. Dissolution data from representative drug product lots 15SXG001UR and DU1506B manufactured at GSIUC and at (b) (4), respectively are shown in **Figure 11** and the *f2* analyses are summarized in **Table 6** and **Table 7**. Data demonstrate that the two proposed commercial manufacturing sites have similar drug products.

Figure 11. Sofosbuvir and Velpatasvir Dissolution Profiles from SOF/VEL Tablets Lot 15SXG001UR (GSIUC) and Lot DU1506B (b) (4)

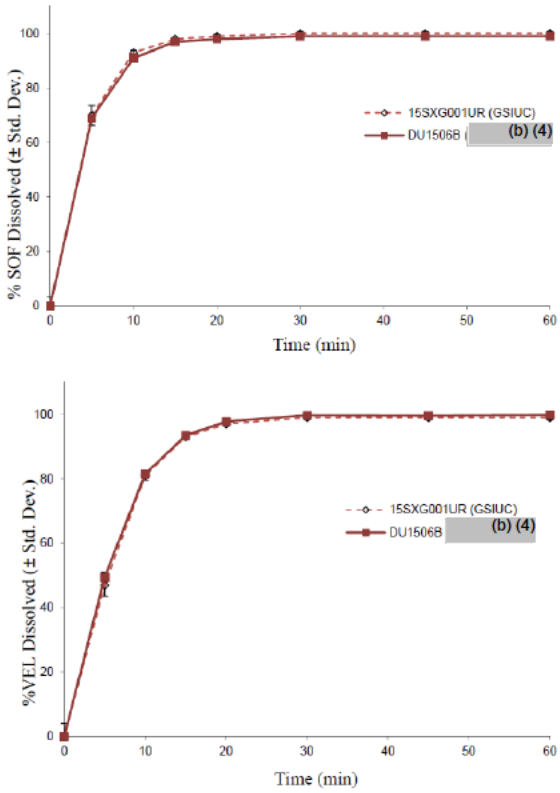


Table 6. Sofosbuvir Dissolution Data Used in *f2* Analysis for Tablets from Each Manufacturing Site

Lot	15SXG001UR (GSIUC)	DU1506B (b) (4)
Time (min)	Percent SOF Dissolved	
5	70	69
10	93	91
15	98	97
f2	88	

Table 7. Sofosbuvir Dissolution Data Used in f2 Analysis for Tablets from Each Manufacturing Site

Lot	15SXG001UR (GSIUC)	DU1506B (b) (4)
Time (min)	Percent VEL Dissolved	
5	47	50
10	81	81
15	93	93
f2	85	

Reviewer's Assessment: **The two proposed commercial DP manufacturing sites are adequately bridged with provided dissolution data and *f2* analyses.**

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature: **ADEQUATE.**

The Applicant conducted a comprehensive dissolution method development to identify the appropriate dissolution apparatus, dissolution medium and volume, surfactant type and concentration, paddle rotation speed, (b) (4) etc. The Applicant tightened the originally proposed dissolution acceptance criterion. The newly proposed dissolution acceptance criterion is supported by the dissolution data of batches tested in pivotal phase 3 clinical trials. Based on our discussion with the process reviewer, the risk in manufacturing batches with (b) (4) has been mitigated by the implementation of appropriate controls. The dissolution specifications shown in the table below are deemed acceptable.

Apparatus	USP Dissolution Apparatus 2 (Paddle Method)
Stirring Speed	75 rpm
Medium	50 nM sodium acetate at pH 5.0 with 0.5% w/v CTAB
Medium Volume	900 mL
Sampling Times	5, 10, 20, 30 and 45 minutes
Acceptance Criteria	Q = (b) (4)% at 20 minutes for both SOF and VEL

The drug product is formulated as immediate release tablet with high solubility of the two APIs in the proposed dissolution medium. The proposed dissolution method has discriminating ability against the (b) (4) are the two factors that have direct impact on the (b) (4). The method does not have discriminating ability against some CPPs (within PARs) and CMAs such as (b) (4) Lacking of discriminating capability against the above parameters is not critical issue for the proposed dissolution method since the manufacturing process will be operated within PARs. In addition, the proposed in-process testing ensures

the quality of (b) (4). It is worth mentioning that the dissolution method discriminates for batches manufactured at the (b) (4)

There are no formulation and process changes for the to-be-market drug product. Data provided demonstrated the similarity of the two proposed commercial drug product manufacturing sites.

NDA 208341 (Sofosbuvir/Velpatasvir Fixed-Dose Combination Tablet (400 mg/100 mg)) is RECOMMENDED FOR APPROVAL from a Biopharmaceutics perspective.

Ge Bai, Ph.D., 02/29/2016
Biopharmaceutics Reviewer
Office of New Drug Product
Division of Biopharmaceutics

Secondary Review Comments and Concurrence:

I concur with the primary reviewer's assessment of the biopharmaceutics section.
Sandra Suarez Sharp, Ph.D., 03/02/2016
Biopharmaceutics Reviewer
Office of New Drug Product
Division of Biopharmaceutics

ASSESSMENT OF MICROBIOLOGY

To assure drug product safety and confirm no microbial contamination during drug product manufacturing, microbial examination will be conducted. Testing will be performed at release and at the beginning and end of shelf-life for the first three commercial and annual commitment lots of drug product (Section 3.2.P.8.2). The acceptance criteria established according to harmonized pharmacopoeial monographs USP <1111> and Ph. Eur. 5.1.4 will be applied.

Reviewer's Assessment: Adequate

The proposed microbial test is adequate for solid oral dosage form.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommended for approval from microbiology perspective

Ying Wang, Ph.D.
2/17/2016

Secondary Review Comments and Concurrence:

I concur.

Upinder Atwal, Ph.D.
Acting Branch Chief
DPA I/Branch III

02/25/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant requests a categorical exclusion from the requirements to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the expected introduction concentration of sofosbuvir and velpatasvir at the point of entry into the aquatic environment, (b) (4) ppb and (b) (4) ppb, respectively, is less than 1 part per billion. The sofosbuvir value takes into account the other sofosbuvir-containing formulations, Sovaldi and Harvoni. To the applicant's knowledge no extraordinary circumstances exist.

Reviewer's Assessment: Adequate. The claim is reasonable and should be accepted. In an e-mail of 3/4/16 James Laurenson, ONDP concurs. There are no hormonal effects in

mammalian species, even at very high doses relative to the EICs.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The claim for a categorical exclusion from the requirement to perform an Environmental Assessment is reasonable and should be accepted. There are no hormonal effects in mammalian species, even at very high doses relative to the EICs. In an e-mail of 3/4/16 James Laurenson, ONDP concurs.

George Lunn, Ph.D. Apr 1, 2016
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. Apr 1, 2016
QAL/CMC-Lead; Branch-III; ONDP; OPQ

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

Labeling & Package Insert

1. Package Insert

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

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 400 mg sofosbuvir and 100 mg velpatasvir

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Epclusa™ (sofosbuvir and velpatasvir) tablets, for oral use	Adequate
Dosage form, route of administration	Tablets, oral	Adequate
Controlled drug substance symbol (if applicable)	NA	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 400 mg sofosbuvir and 100 mg velpatasvir	Adequate

Conclusion: Adequate.

(b) "Full Prescribing Information" Section

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

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	400 mg sofosbuvir and 100 mg velpatasvir	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side	Adequate

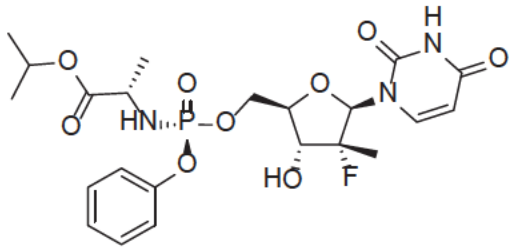
Conclusion: Adequate

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

Epclusa is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase and velpatasvir is an NS5A inhibitor.

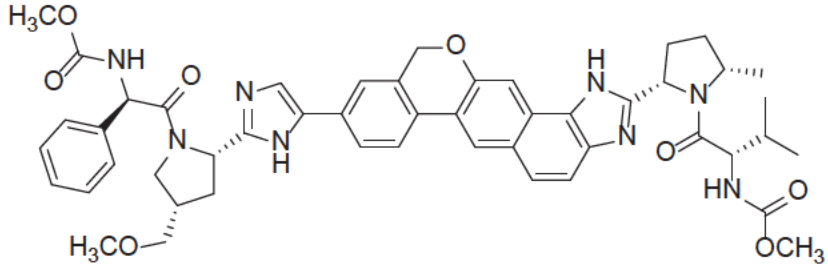
Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir. The tablets include the following inactive ingredients: copovidone, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablets are film-coated with a coating material containing the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide red.

Sofosbuvir: The IUPAC name for sofosbuvir is (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:

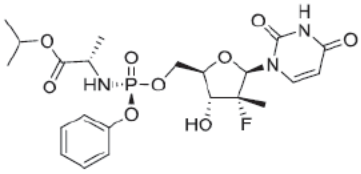


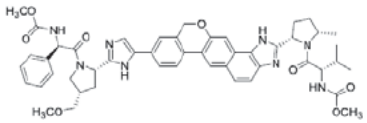
Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37°C and is slightly soluble in water.

Velpatasvir: The IUPAC name for velpatasvir is Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-*d*]imidazol-9-yl}-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0. It has the following structural formula:



Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Epclusa™ (sofosbuvir and velpatasvir) tablets, for oral use	Adequate
Dosage form and route of administration	Tablets, oral	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	NA	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	The tablets include the following inactive ingredients: copovidone, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablets are film-coated with a coating material containing the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide red.	Adequate
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase and velpatasvir is an NS5A inhibitor.	Adequate
Chemical name, structural formula, molecular weight	Sofosbuvir: The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular weight of 529.45. It has the following structural formula:  Velpatasvir: The IUPAC name for velpatasvir is Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]n	Adequate

	aphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular weight of 883.0. It has the following structural formula: 	
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37oC and is slightly soluble in water. Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.	Adequate

Conclusion: Adequate

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

Epclusa tablet (b) (4) pink, diamond-shaped, film-coated (b) (4), debossed with "GSI" on one side and "7916" on the other (b) (4). Each bottle contains 28 tablets (NDC 61958-2201-1), polyester coil, and is closed with a child resistant closure.

Store below 30 ˚C (86 ºF).

- Dispense only in original container

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir.	Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 28 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side	Adequate
Special handling (e.g., protect from light, do not freeze)	Dispense only in original container	Adequate
Storage conditions	Store below 30 ˚C (86 ºF)	Adequate

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)	Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404	Adequate

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

The US container label is as follows.

(b) (4)

The Access container label is as follows.

(b) (4)

Reviewer's Assessment: Adequate.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Epclusa	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Sofosbuvir, velpatasvir tablets 400 mg / 100 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral. Not on container label	Adequate
Net contents* (21 CFR 201.51(a))	28 tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not on container label. This is acceptable**	Adequate
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate
Storage (not required)	Store below 30°C (86°F) (see insert)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 61958-2201-1	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404	Adequate
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

Conclusion: Adequate

2) Carton Labeling
(Carton is for the Access product only)

(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))	Epclusa	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Sofosbuvir, velpatasvir tablets 400 mg / 100 mg	Adequate
Net contents (21 CFR 201.51(a))	28 tablets	Adequate
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	NA	
Sterility Information (if applicable)	NA	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	Adequate
Storage Conditions	Store below 30°C (86°F)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	61958-XXXX-X	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present	Adequate
Name of manufacturer/distributor	Manufactured for: Gilead Sciences, Inc., Foster City, CA 94404. Manufactured by: (b) (4)	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Present	Adequate
(b) (4)		

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	NA	

Conclusion: Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
The labeling is acceptable from the Product Quality Perspective. Our recommendations for labeling negotiations are listed in the Executive Summary.

George Lunn, Ph.D. Apr 1, 2016
DP Reviewer; Branch-III; DNDP-I; ONDP; OPQ

Secondary Review Comments and Concurrence:
I concur with Dr. Lunn's recommendation.

Stephen Miller, Ph.D. Apr 1, 2016
QAL/CMC-Lead; Branch-III; ONDP; OPQ

II. List of Deficiencies To Be Communicated

Drug Substance
Drug Product
Process
Facility
Biopharmaceutics
Microbiology
Environmental
Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

Final Risk Table for Sofosbuvir and Velpatasvir Tablets

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		L		L	(b) (4)
Physical stability (solid state)		M		L	Supporting data show API form is inherently stable and shows (b) (4) .
Content uniformity	(b) (4)	L		L	
Microbial limits		L		L	
Dissolution – BCS Class III & IV	• (b) (4) • Permissive dissolution acceptance criteria	M	• (b) (4) • Evaluation and comparison of dissolution profiles of clinical and clinical stability batches • Evaluation and recommendation of dissolution acceptance criteria	L	One API (SOF) has high solubility. The other API (VEL) has low solubility (b) (4) The drug product is formulated as immediate release tablet. (b) (4) The proposed dissolution method has discriminating ability against the (b) (4) The recommended stringent dissolution acceptance criteria will ensure the quality of the drug product. Overall, the risk of dissolution remains low after review of dissolution method and dissolution data.
(b) (4)		M		L	
Drug Product Impurity Control		L		L	
Risk Factors associated with Patient Use	Moderately-sized tablet (10mm x 20 mm); no score or dispersing instructions	L		L	

NDA/BLA » NDA 208341

NDA-208341-ORIG-1

Project Actions

Project Owner
Linda Onaga
Senior Regulatory Project Manager

Status	Condition	Planned Completion	Percent Complete
Current	At Risk	Nov 19, 2016	69%

Project Summary | Project Details | Application Life Cycle | Application History | Inspection View | Tasks | **Submission Facility Status View**

As of Jun 28, 2016 9:22 am GMT

Submission Overall Manufacturing Facility Status

Overall Status	Completion Date	Project Name
Approve	6/13/2016	NDA-208341-ORIG-1

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Global ID	Facility Name	Profile Code	Associatic
Approve Facility	6/13/2016	NDA-208341-ORIG-1				(b) (4)	NEC NOT ELSEWHERE CLASSIFIED	ACTIVE
Approve Facility	5/31/2016	NDA-208341-ORIG-1	3006709727	989325600	16014	GILEAD SCIENCES LIMITED	TCM TABLETS. PROMPT RELEASE	ACTIVE
Approve Facility	5/31/2016	NDA-208341-ORIG-1				(b) (4)	NEC NOT ELSEWHERE CLASSIFIED	ACTIVE
Approve Facility	12/2/2015	NDA-208341-ORIG-1	3001027806	207452996	67878	GILEAD ALBERTA ULC	CSN NON-STERILE API BY CHEMIC...	ACTIVE
Approve Facility	12/2/2015	NDA-208341-ORIG-1				(b) (4)	TCM TABLETS. PROMPT RELEASE	ACTIVE
Approve Facility	12/2/2015	NDA-208341-ORIG-1					CSN NON-STERILE API BY CHEMIC...	ACTIVE
Approve Facility	12/2/2015	NDA-208341-ORIG-1					CSN NON-STERILE API BY CHEMIC...	ACTIVE
Approve Facility	11/16/2015	NDA-208341-ORIG-1	1000523075	185049848	63091	GILEAD SCIENCES INC	CTL CONTROL TESTING LABORATOR...	ACTIVE
Approve Facility	11/13/2015	NDA-208341-ORIG-1				(b) (4)	CTL CONTROL TESTING LABORATOR...	ACTIVE
Approve Facility	11/13/2015	NDA-208341-ORIG-1					CSN NON-STERILE API BY CHEMIC...	ACTIVE
Approve Facility	11/3/2015	NDA-208341-ORIG-1					CTL CONTROL TESTING LABORATOR...	ACTIVE
Approve Facility	11/3/2015	NDA-208341-ORIG-1					CSN NON-STERILE API BY CHEMIC...	ACTIVE
Cancelled	11/3/2015	NDA-208341-ORIG-1	3006709727	989325600	16014	GILEAD SCIENCES LIMITED	(b) (4)	ACTIVE
Cancelled	10/30/2015	NDA-208341-ORIG-1				(b) (4)	TCM TABLETS. PROMPT RELEASE	ACTIVE
Cancelled	10/30/2015	NDA-208341-ORIG-1					TCM TABLETS. PROMPT RELEASE	ACTIVE
Approve Facility	10/30/2015	NDA-208341-ORIG-1	2082946	941715849	14251	GILEAD SCIENCES INC	TCM TABLETS. PROMPT RELEASE	ACTIVE
Approve Facility	10/30/2015	NDA-208341-ORIG-1				(b) (4)	CTL CONTROL TESTING LABORATOR...	ACTIVE
No Further Evaluation	10/30/2015	NDA-208341-ORIG-1					TCM TABLETS. PROMPT RELEASE	PENDING