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APPLICATION NUMBER:

214187Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDAs(Supplement Number)	214187(original), 208341(S-17)
Link to EDR	NDA214187 - (0001), NDA208341 - (0156)
Submission Date	12/15/2020
Submission Type	Priority
Brand Name	Epclusa
Generic Name	Sofosbuvir/Velpatasvir
Dosage Form and Strength	Oral Pellets; 200/50 mg & 150/37.5 mg
Proposed Indication	Treatment of chronic hepatitis C in pediatrics.
Applicant	Gilead Sciences, Inc.
Associated INDs	IND118605, IND115670, IND106739
OCP Review Team	Abhay Joshi, Elyes Dahmane, Jihye Ahn, Jenny Zheng

Contents

1. EXECUTIVE SUMMARY

This submission is an original NDA for a new oral EPCLUSA® pellets (also referred as granules) proposed to be used for the treatment of hepatitis C virus (HCV) infection in pediatric patients (HCV patients). EPCLUSA® is a fixed combination drug product for sofosbuvir (SOF) and velpatasvir (VEL). SOF is a HCV nonstructural protein 5B (NS5B) polymerase inhibitor and VEL is an HCV NS5A inhibitor. Two SOF/VEL fixed dose combination tablet formulations (400 mg/100 mg and 200 mg/50 mg tablets) are currently approved by the FDA for the treatment of adults and pediatrics 6 years of age and older or weighing at least 17 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis. For patients with decompensated cirrhosis, EPCLUSA's use is recommended in combination with ribavirin.

This submission is also in accordance to a Post Marketing Requirement (PMR 3092-2) under the Pediatric Research Equity Act (PREA) for NDA 208341 (EPCLUSA, SOF/VEL tablets). The PMR was to conduct a study to evaluate the pharmacokinetics, safety, and treatment response (using sustained virologic response) of SOF/VEL in pediatrics 3 years to 12 years with chronic HCV infection.

With this submission, the Applicant proposes to extend the indication for EPCLUSA for pediatric HCV patients down to 3 years of age and proposes revisions to the currently recommended pediatric dosing regimen as summarized in **Table 1**. The Applicant also proposes revisions to pharmacokinetic information included in the clinical pharmacology sections of EPCLUSA labeling. The Applicant's proposals are being supported based on the findings from:

- A Phase 2 study (Study GS-US-342-1143) that evaluated the safety and efficacy of the currently approved SOF/VEL tablet formulations and the to-be-marketed pellet formulation in adolescents and children with chronic HCV
- A Phase 1 relative bioavailability study (Study GS-US-342-1142) that compared the (b) (4) SOF/VEL pellet formulation (at the 400/100 mg dose; under fasted and fed conditions) to the approved 400 mg/100 mg tablet formulation in healthy adults
- An updated population PK (POP-PK) analysis (Report CTRA-2020-1044) that characterized and estimated individual exposures of SOF, SOF metabolites (GS-331007, GS-566500), and VEL in the pediatrics.

Table 1: The Approved Dosage and the Applicant's Proposed Changes (in red) for Pediatrics

(b) (4)

Source: Adapted from the annotated draft label submitted by the Applicant

The key clinical pharmacology review issues are listed below:

(1) Interchangeability between tablets and pellets
(2) SOF/VEL dosing regimen for pediatric HCV patients ≥ 3 years
(3) Labeling revisions to the clinical pharmacology sections

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information provided by the Applicant in NDA214187 as well as NDA208341 and recommends approval for the new EPCLUSA oral pellet formulation.

1.1. Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Interchangeability Between Tablets and Pellets

The Applicant proposes interchangeable use of tablets and pellets and this proposal is primarily supported by the findings from a Phase 1 relative bioavailability study (Study GS-US-342-1142). The Phase 1 study compared the to-be-marketed SOF/VEL pellet formulation to the currently approved SOF/VEL tablet formulation (400/100 mg) in healthy adults. The findings from Study GS-US-342-1142 show that the exposures to SOF, GS-566500, GS-331007, and VEL from the to-be-marketed SOF/VEL pellet formulation was comparable to the SOF/VEL tablet formulation under fasted conditions. The comparison of exposures was based on the determination if geometric least-squares mean (GLSM) and associated 90% confidence intervals (CI) for drug exposure parameter estimates (AUC and Cmax) contained within the traditionally used boundaries of 80% to 125% for bioequivalence studies. The AUC estimates for SOF were also comparable between the SOF/VEL pellet and tablet formulations, however, the mean of SOF Cmax estimate from the SOF/VEL pellet formulation was approximately 20% lower compared to the tablet formulation (GLSM ratio: 0.8, 90% CI: 0.72-0.9). The reduced SOF Cmax from the new pellet formulation is not expected to be clinically relevant for the pediatric patients ≥ 3-6 years of age. The Applicant proposes that the SOF/VEL pellet formulation can be administered without regard to

food. The Applicant's proposal is based on the findings from Study GS-US-342-1142 that assessed the effect of food on the systemic exposure to SOF, GS-331007, GS-566500, and VEL following the administration of a single SOF/VEL dose of 400/100 mg after a high fat meal in healthy adult subjects. Given that the currently approved tablet formulations are recommended to be taken with or without food, the findings reported on food-effect for pellet formulation from Study GS-US-342-1142 were compared against the reported findings on food-effect for tablet formulation in the Clinical Pharmacology Biopharmaceutics Review (**Link**). The comparison shows that the food-effect on the PK of SOF/VEL is comparable between the new pellet formulation and the approved tablet formulation (**Table 6**). Therefore, the Applicant's proposal that the to-be-marketed SOF/VEL pellet formulation can be administered without regard to food is acceptable. It is noteworthy that in Study GS-US-342-1143, which evaluated the safety and efficacy of the new pellet formulation, SOF/VEL doses were administered in pediatric patients without regard to food. Please refer to **Section 3.2** for additional details on Study GS-US-342-1142 findings.

An inspection for the bioanalytical sites was also requested for Study GS-US-342-1142 and Study GS-US-342-1143. The Office of Study Integrity and Surveillance (OSIS) concluded that an inspection of the analytical site is not warranted at this time (OSIS review, NDA214187 dated 02/18/2021). The bioanalytical site (b) (4)) for Studies GS-US-342-1142 and GS-US-342-1143 was inspected in (b) (4) (OSIS review, (b) (4), dated 02/15/2019) and the final classification was NAI. The OSIS reviewer concluded "…the data from the audited studies are reliable to support a regulatory decision." Therefore, we determined that the favorable inspection results at the bioanalytical site under (b) (4) can be applied to this submission and we accept PK results from the abovementioned studies.

2.2. SOF/VEL Dosing Regimen for Pediatric Patients ≥ 3 Years

The results from the Applicant's population PK analysis and simulations suggest that the proposed weight band-based dosing regimen of 150 mg/37.5 mg once daily for SOF/VEL in pediatric patients with body weight < 17 kg is appropriate. The proposed regimen provides exposure comparable to the exposure expected from the already approved dosing in pediatric patients with body weight ≥17 kg and within the range of the observed exposures in adults. Please see **Section 3.4** for additional details.

2.3. Proposed Labeling Changes

The Applicant proposed labeling changes related to clinical pharmacology aspects are summarized in **Table 2** below along with the clinical pharmacology assessments.

Table 2: Prescription Drug Labeling Changes (Selected)

Summary of Significant Labeling Changes		
Section	**Applicant Proposed Changes**	**Clinical Pharmacology Assessment**
INDICATIONS AND USAGE	- Lower the minimum age for treatment eligibility from 6 years to 3 years and remove lower weight cutoff of at least 17 kg	The proposed changes are acceptable. See **Section 2.2** for additional details.
DOSAGE AND	- Corresponding changes to align with INDICATIONS	The proposed changes

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