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APPLICATION NUMBER:

212477Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW	
NDA Numbers (SDN)	205834 (835) S-29 212477 (1)
Link to EDR	\\CDSESUB1\evsprod\NDA205834\205834.enx \\CDSESUB1\evsprod\NDA212477\212477.enx
Submission Date	02/28/2019
Submission Types	Prior Approval Efficacy Supplement (NDA 205834) Original NDA (NDA 212477)
Brand Name	HARVONI®
Generic Name	Ledipasvir/Sofosbuvir (LDV/SOF)
Dosage Regimen	• Adults and pediatric patients 12 years and older: One tablet (90 mg of LDV and 400 mg of SOF) taken orally QD with or without food. • Pediatric patients 3 years (b) (4) 33.75/150 mg to 90/400 mg LDV/SOF tablet or oral granules per day with or without food.
Route of Administration	Oral
Proposed Indication	Treatment of Hepatitis C Virus (HCV) infection
Applicant	Gilead Sciences, Inc.
OCP Review Team	Hazem E. Hassan, PhD, MS, RPh, RCDS Ruojing Li, PhD Chao Liu, PhD Su-Young Choi, Pharm D, PhD

Table of Contents

1. Executive summary

Harvoni® tablet is a fixed-dose combination (FDC) of LDV, an HCV NS5A inhibitor, and SOF, an HCV nucleotide analog NS5B polymerase inhibitor. HARVONI® is indicated for the treatment of HCV in adults and pediatrics (12 years of age and older or weighing at least 35 kg). The recommended dosage in adults and pediatric patients 12 years and older is one tablet (90 mg of LDV and 400 mg of SOF) taken orally once daily with or without food.

The Applicant submitted a Prior Approval Efficacy Supplement (NDA 205834) and an original NDA (212477) in support of expanding the indication of HARVONI® to pediatric patients 3 to < 12 years. The proposed pediatric dosages for patients 3 years or older are as follows:

Proposed Dosing for Pediatric Patients 3 Years and Older Using HARVONI Tablets or Oral Granules

Body Weight (kg)	Dosing of HARVONI Tablets or Oral Granules	HARVONI Daily Dose
at least 35	one 90 mg/400 mg tablet once daily or two 45 mg/200 mg tablets once daily or two 45 mg/200 mg packets of granules once daily	90 mg/400 mg per day
17 to less than 35	one 45 mg/200 mg tablet once daily or one 45 mg/200 mg packet of granules once daily	45 mg/200 mg per day
less than17	one 33.75 mg/150 mg packet of granules once daily	33.75 mg/150 mg per day

The basis of approval of the current application is extrapolation of the efficacy from adult subjects by demonstrating comparable systemic exposures of SOF, GS-331107 (SOF major inactive metabolite) and LDV between adults and pediatric patients with HCV infection. The proposed dosage regimens were supported by PK, safety and efficacy data from study GS-US-337-1116 in HCV infected pediatric patients. The LDV/SOF FDC doses employed in this study targeted systemic exposures similar to those observed in adults at the approved dose (LDV/SOF 90/400 mg). Results from this study indicated that there were no clinically relevant differences between SOF, GS-331107 and LDV exposures (AUC_{tau} or C_{max}) in pediatric subjects and exposures observed in the adult Phase 2/3 studies. Population PK analyses and simulations were conducted to evaluate SOF, GS-331007 and LDV exposures based on proposed weight band-based dosing regimens. The simulation analyses indicated that exposures in pediatrics 3 to < 12 years are comparable to those in adults.

The applicant developed and evaluated two pediatric formulations, a low strength HARVONI tablet (45/200 mg) and oral granules (SOF/LDV 45/200 mg and 33.75/150 mg). The applicant requested a biowaiver for the low strength HARVONI® 45/200-mg tablet and conducted study GS-US-337-2091 to evaluate the bioavailability (BA) of the granules relative to the approved tablet formulation, and the food effect on the granules. Overall, there were no clinically significant differences in the exposures of SOF, GS-331107 and LDV following a) administration of granules and tablets under fasted condition and b) administration of granules under fed and fasted conditions.

2. Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that the proposed weight-based dosage regimens in pediatrics are acceptable. This original NDA and pediatric efficacy supplement are *approvable* from a clinical pharmacology perspective.

3. Labeling Recommendations

The following clinical pharmacology related information will be added in HARVONI® USPI:

Section 2 Dosage and Administration

Sub-Section 2.4 Recommended Dosage in Pediatric Patients 3 years of Age and Older

- Add recommended weight-based doses of HARVONI®.
- Add recommended weight-based doses of Ribavirin (RBV) to be given in combination with HARVONI®.

Section 8 Specific Population

Sub-Section 8.4 (Pediatric Use)

- Add the summary of findings in study GS-US-337-1116.

Section 12 Clinical Pharmacology

Sub-Section 12.3 Pharmacokinetics

- Update the PK table to include exposure parameters of HARVONI® in pediatrics 3 years of age and older based on the findings in study GS-US-337-1116.

4. Summary of Important Clinical Pharmacology Findings

Study GS-US-337-1116:

- Comparison of SOF, GS-331007, and LDV exposures between pediatric subjects 3 to < 12 years old and adults indicated that there were no clinically significant differences in exposures between pediatrics and adults. The proposed weight band based dosing is acceptable.

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