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APPLICATION NUMBER:

205834Orig1s007, s008, s009

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 205,834
Supporting document/s: S007, S008, S009
Applicant's letter date: August 26, 2015
CDER stamp date: August 26, 2015
Product: Harvoni™ is a fixed-dose combination (FDC) tablet of ledipasvir (LDV), an HCV NS5A inhibitor, and sofosbuvir (SOF), an HCV nucleotide analog NS5B polymerase inhibitor
Indication: Harvoni™ is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection
Applicant: Gilead Sciences
Review Division: Division of Antiviral Products
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1 Executive Summary

1.1 Introduction

Harvoni™, a once daily fixed-dose combination (FDC) tablet containing ledipasvir and sofosbuvir, is indicated for treatment of chronic hepatitis C virus (HCV) genotype 1 infection in adult patients. Ledipasvir (LDV, GS-5885) is a specific inhibitor of nonstructural protein 5A (NS5A) of HCV that has displayed potent inhibition of HCV replication *in vitro*. Sofosbuvir (SOF, GS-7977) is a nucleotide prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that is converted intracellularly to the active uridine triphosphate (GS-461203) within tissues. GS-461203 is a specific inhibitor of nonstructural protein 5B (NS5B) of HCV that has displayed potent inhibition of HCV replicon ribonucleic acid (RNA) replication *in vitro*. SOF (as a component of a combination antiviral treatment regimen) was approved for marketing in the U.S. in December 2013.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical safety studies were submitted with these supplements. PLLR-related edits were made to the Harvoni™ label (refer to Section 1.3.3 for suggested language).

1.3 Recommendations

1.3.1 Approvability

Not applicable. Harvoni™ (FDC tablet containing LDV and SOF) was approved for marketing in the U.S. in October 2014.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No adequate human data are available to establish whether or not HARVONI poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of HARVONI (ledipasvir or sofosbuvir) at exposures greater than those in humans at the recommended human dose (RHD) [see *Data in (8.1)*]. During organogenesis in the rat and rabbit, systemic exposures (AUC) to ledipasvir were approximately 4 (rats) and 2 (rabbits) times the exposure in humans at the RHD, while exposures to the predominant circulating metabolite of sofosbuvir (GS-331007) were ≥ 3 (rats) and 7 (rabbits) times the exposure in humans at the RHD. In rat pre/postnatal development studies, maternal systemic exposures (AUC) to ledipasvir and GS-331007 were approximately 5 and 7 times, respectively, the exposure in humans at the RHD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

If HARVONI is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.

Data

Animal Data

Ledipasvir: Ledipasvir was administered orally to pregnant rats (up to 100 mg/kg/day) and rabbits (up to 180 mg/kg/day) on gestation days 6 to 18 and 7 to 20, respectively, and also to rats (oral doses up to 100 mg/kg/day) on gestation day 6 to lactation/postpartum day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. Systemic exposures (AUC) to ledipasvir were ≥ 4 (rats) and 2 (rabbits) times the exposure in humans at the RHD.

Sofosbuvir: Sofosbuvir was administered orally to pregnant rats (up to 500 mg/kg/day) and rabbits (up to 300 mg/kg/day) on gestation days 6 to 18 and 6 to 19, respectively, and also to rats (oral doses up to 500 mg/kg/day) on gestation day 6 to lactation/postpartum day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. Systemic exposures (AUC) to the predominant circulating metabolite of sofosbuvir (GS-331007) were ≥ 3 (rats) and 7 (rabbits) times the exposure in humans at the RHD, with exposures increasing during gestation from approximately 3 to 6 (rats) and 7 to 17 (rabbits) times the exposure in humans at the RHD.

8.2 Lactation

Risk Summary

It is not known whether HARVONI and its metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. When administered to lactating rats, ledipasvir was detected in the plasma of nursing pups likely due to the presence of ledipasvir in milk, without clear effects on nursing pups [see Data in (8.2)]. The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the breastfed child from HARVONI or from the underlying maternal condition.

If HARVONI is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use during lactation.

Data

Ledipasvir: No effects of ledipasvir on growth and postnatal development were observed in nursing pups at the highest dose tested [see *Data in (8.1)*]. Maternal systemic exposure (AUC) to ledipasvir was approximately 5 times the exposure in humans at the RHD. Although not measured directly, ledipasvir was likely present in the milk of lactating rats, since systemic exposure (AUC) to ledipasvir of approximately 25% that of maternal exposure was observed in nursing pups on lactation day 10.

Sofosbuvir: No effects of sofosbuvir on growth and postnatal development were observed in nursing pups at the highest dose tested [see *Data in (8.1)*]. Maternal systemic exposure (AUC) to the predominant circulating metabolite of sofosbuvir (GS-331007) was approximately 7 times the exposure in humans at the RHD, with exposure of approximately 2% that of maternal exposure observed in nursing pups on lactation day 10. In a lactation study, sofosbuvir metabolites (primarily GS-331007) were excreted into the milk of lactating rats following administration of a single oral dose of sofosbuvir (20 mg/kg) on lactation day 2, with milk concentrations of approximately 10% that of maternal plasma concentrations observed 1 hour post-dose.

8.3 Females and Males of Reproductive Potential

If HARVONI is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

2 Drug Information

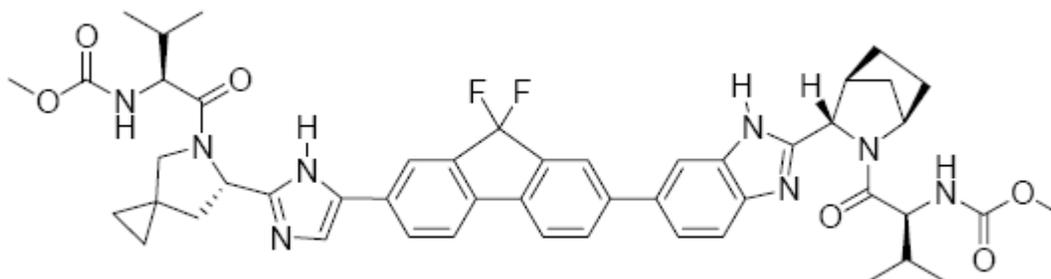
2.1 Drug

2.1.1 Ledipasvir

CAS Registry Number	1256388-51-8
Generic Name	Ledipasvir (LDV)
Code Name	GS-5885
Chemical Name	Methyl [(2S)-1-[(6S)-6-[5-(9,9-difluoro-7-{2-[(1R,3S,4S)-2-[(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl]-2-azabicyclo[2.2.1]hept-3-yl]-1H-benzimidazol-6-yl]-9H-fluoren-2-yl]-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl]-3-methyl-1-oxobutan-2-yl] carbamate (IUPAC)

Molecular Formula/Molecular Weight $C_{49}H_{54}F_2N_8O_6$ //889.00 g/mol

Structure



Pharmacologic Class HCV NS5A inhibitor

2.1.2 Sofosbuvir

CAS Registry Number 1190307-88-0

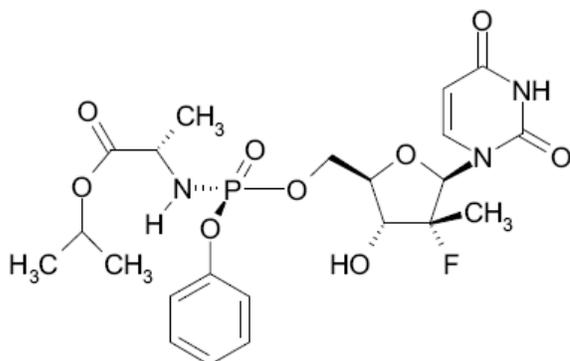
Generic Name Sofosbuvir (SOF)

Code Name GS-7977 (PSI-7977)

Chemical Name (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 (IUPAC)

Molecular Formula/Molecular Weight $C_{22}H_{29}FN_3O_9P$ /529.4^(b)₍₄₎ g/mol

Structure



Pharmacologic Class HCV nucleotide analog NS5B polymerase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND-108,214 (for LDV), IND-104,522, IND-106,739 and NDA-204,671 (for SOF) and IND-115,268 (for LDV & SOF FDC).

2.3 Drug Formulation

LDV/SOF fixed dose combination (FDC) tablets are orange, biconvex, film-coated, diamond shaped tablets containing 90 mg of LDV and 400 mg of SOF (refer to Sponsor table below).

Table 1: Composition of LDV/SOF FDC tablets

Component	Composition (% w/w)	Unit Formula (mg/tablet)	Reference Quality Standards	Function
(b) (4)				
Sofosbuvir ^a	40.0	400.0	In-house	Active Ingredient
Ledipasvir ^{b,e,d,e}	9.0	90.0	In-house	Active Ingredient
Copovidone ^{d,e}	(b) (4)			
(b) (4)				
Lactose Monohydrate ^{a,d}				
Microcrystalline Cellulose				
Croscarmellose Sodium				
Collodial Silicon Dioxide				
Magnesium Stearate				
(b) (4)				
Total	100.0	1000.0	--	--
Film-Coat				
(b) (4)				
(b) (4)				

2.4 Comments on Novel Excipients

Not applicable. All excipients are compendial.

2.5 Comments on Impurities/Degradants of Concern

Refer to original Pharmacology/Toxicology review for NDA-205,834.

2.6 Proposed Clinical Population and Dosing Regimen

LDV/SOF FDC is indicated for the treatment (single tablet once a day) of chronic hepatitis C (CHC) genotype 1 infection for 12 to 24 weeks in adult patients.

2.7 Regulatory Background

Harvoni™ (FDC tablet containing LDV and SOF) was approved for marketing in the U.S. in October 2014.

3 Studies Submitted

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Refer to original Pharmacology/Toxicology review for NDA-205,834.

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/s/

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01/29/2016

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