GILEAD | Medical Information

Epclusa® (SOF/VEL), Harvoni® (LDV/SOF), Sovaldi® (SOF), and Vosevi® (SOF/VEL/VOX) Concomitant Treatment for Active Tuberculosis

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]), Harvoni® (ledipasvir/sofosbuvir [LDV/SOF]), Sovaldi® (sofosbuvir [SOF]), or Vosevi® (sofosbuvir/velpatasvir/voxilaprevir [SOF/VEL/VOX]), in patients receiving concomitant treatment for active tuberculosis (TB).

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www.gilead.com/-/media/files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi;
www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.

Summary

Product Labeling

SOF/VEL/VOX is contraindicated with rifampin.[1]

P-gp inducers (eg, rifampin): May alter the concentrations of SOF and/or VEL. Use of SOF/VEL, LDV/SOF, or SOF with P-gp inducers is not recommended.[2-4]

Clinical Data on SOF-Based Regimens and Active TB Treatment

An observational study evaluated the prevalence of chronic HCV and outcomes with SOF-based HCV treatment during MDR-TB treatment.[5]

- During MDR-TB treatment, 30 patients began treatment for HCV (SOF + DCV or LDV/SOF), and 23 of the 24 patients (95.8%) with HCV PCR data at the SVR12 time point achieved SVR12.
- One patient (3.3%) experienced an SAE of an allergic reaction that was likely related to SOF + DCV treatment.

Product Labeling

Contraindications[1]

SOF/VEL/VOX is contraindicated with rifampin.

Warnings and Precautions[2-4]

Risk of reduced therapeutic effect due to use with P-gp inducers

The concomitant use of SOF/VEL, LDV/SOF, and SOF and P-gp inducers may significantly decrease SOF, LDV, and/or VEL plasma concentrations and may lead to a reduced therapeutic effect of SOF/VEL, LDV/SOF, and SOF. Therefore, the use of SOF/VEL, LDV/SOF, and SOF with P-gp inducers (eg, rifampin) is not recommended.

Drug Interactions[1-4]

Potential for other drugs to affect SOF/VEL, LDV/SOF, and SOF

SOF, LDV, VEL, and VOX are substrates of the drug transporter P-gp, while GS-331007 is not.

Established and potentially significant drug interactions

Table 1 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with SOF/VEL, LDV/SOF, SOF, and SOF/VEL/VOX and the components of SOF/VEL, LDV/SOF, SOF, and SOF/VEL/VOX (SOF, LDV, VEL, and VOX) as individual agents, or are predicted drug interactions that may occur with SOF/VEL, LDV/SOF, SOF, and SOF/VEL/VOX.

Table 1. Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[1-4a]

Antimycobacterials: Drug Name	Effect on Concentration	Clinical Effect/Recommendation
Rifampin[b]	Decreases SOF Decreases GS-331007 Decreases VEL Decreases LDV Decreases VOX (multiple dose) Increases VOX (single dose)	• Coadministration with rifampin is contraindicated with SOF/VEL/VOX • Coadministration is not recommended with SOF/VEL, LDV/SOF, or SOF
Rifabutin[b] Rifapentine	Decrease SOF Decrease GS-331007 Decrease VEL Decrease LDV Decrease VOX	• Coadministration is not recommended

[a]This table is not all-inclusive. [b]These interactions have been studied in healthy adults.

Clinical Pharmacology

Pharmacodynamics[1-4]

Cardiac electrophysiology

The effect of SOF 400 mg (recommended dosage) and 1200 mg (3 times the recommended dosage) on QTc interval was evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT trial in 59 healthy subjects. At a dosage 3 times the maximum recommended dose, SOF does not prolong QTc to any clinically relevant extent.

The effect of VEL 500 mg (5 times the recommended dosage) was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT trial. At a dose 5 times the recommended dose, VEL does not prolong QTc interval to any clinically relevant extent.

The effect of LDV 120 mg twice daily (2.67 times the maximum recommended dosage) for 10 days on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three-period crossover thorough QT trial in 59 healthy subjects. At the dose of 120 mg twice daily (2.67 times the maximum recommended dosage), LDV does not prolong QTc interval to any clinically relevant extent.

The effect of VOX 900 mg (9 times the recommended dosage) was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT trial. At a dose 9 times the recommended dose, VOX does not prolong QTc interval to any clinically relevant extent.

PK[1-4]

The effects of coadministered drugs on the exposure of SOF, GS-331007, VEL, LDV, and VOX are shown in Table 2.

Table 2. Drug Interactions: Changes in PK Parameters for SOF, GS-331007, VEL, LDV, and VOX in the Presence of the Coadministered Drug[1-3a]

Coadministered Drug		SOF, VEL, LDV, VOX		N	GMR (90% CI) of SOF, GS-331007, VEL, LDV, and VOX PK With/Without Coadministered Drug; No Effect=1			
Drug	Dosage	Active Component	Dosage		Component	C_{max}	AUC	C_{min}
Rifabutin	300 mg once daily	SOF	400 mg single dose	20	SOF	0.64 (0.53–0.77)	0.76 (0.63–0.91)	N/A
					GS-331007	1.15 (1.03–1.27)	1.03 (0.95–1.12)	N/A
Rifampin	600 mg once daily	SOF	400 mg single dose	17	SOF	0.23 (0.19–0.29)	0.28 (0.24–0.32)	N/A
					GS-331007	1.23 (1.14–1.34)	0.95 (0.88–1.03)	N/A
		VEL	100 mg single dose	12	VEL	0.29 (0.23–0.37)	0.18 (0.15–0.22)	N/A
		LDV	90 mg single dose[b]	31	LDV	0.65 (0.56–0.76)	0.41 (0.36–0.48)	N/A
		VOX	100 mg single dose	24	VOX	0.91 (0.76–1.1)	0.27 (0.23–0.31)	N/A
	600 mg single dose	VEL	100 mg single dose	12	VEL	1.28 (1.05–1.56)	1.46 (1.17–1.83)	N/A
		VOX	100 mg single dose	24	VOX	11.1 (8.23–14.98)	7.91 (6.2–10.09)	N/A

Abbreviations: AUC=area under the concentration-time curve; C_{max}=maximum concentration; C_{min}=minimum concentration; GMR=geometric mean ratio.
[a]All interaction studies were conducted in healthy volunteers.
[b]This study was conducted in the presence of 2 other investigational HCV direct-acting agents.

Clinical Data on SOF-Based Regimens and Active TB Treatment

Observational Study of SOF-Based Treatment in Patients With MDR-TB[5]

Study design

An observational study was conducted to determine the prevalence of chronic HCV and the effectiveness and safety of SOF-based HCV treatment in the setting of MDR-TB disease in Armenia. Adult patients who were diagnosed with chronic HCV between January 2016 and December 2018 were followed until June 2019. All patients who began treatment for MDR-TB were offered HCV Ab testing, followed by HCV PCR testing. After December 2016, patients with chronic HCV were offered 12 weeks of treatment with SOF 400 mg + DCV 60 mg (DCV could be increased to 90 mg when patients were also receiving EFV or NVP) or LDV/SOF 90 mg/400 mg. For patients with HCV GT 3a and advanced fibrosis (FibroScan >14.5 kPa), the length of treatment was extended to 24 weeks, and RBV was added to the regimen.

Patients with end-stage liver disease; hepatocellular carcinoma; terminal disease; HIV viral load >1000 copies/mL; severe, uncontrolled psychiatric disease; and Hgb level <9 g/dL at baseline (in those who received RBV-containing regimens) were excluded.

The effectiveness endpoint was SVR12, and the safety endpoint was the incidence of AEs of clinical significance, as well as SAEs during treatment and up to 12 weeks after treatment. Follow-up was performed monthly, at EOT, and at SVR12. Data from patients who began treatment before May 2018 were reviewed retrospectively, and, after this date, patients were followed prospectively.

Patient disposition and demographics

Of the 322 patients with MDR-TB who began treatment during the study period, 266 patients (82.6%) underwent HCV Ab testing. Of the patients who underwent testing, 78 patients (29.3%) were HCV Ab+, and 70 patients (89.4%) underwent HCV PCR testing, including 20 patients who began MDR-TB treatment before the study period but had positive HCV PCR results during the study period. Forty patients had positive HCV PCR tests and began HCV treatment during the study period. During MDR-TB treatment, 30 patients began treatment for HCV, and 29 completed their treatment (1 was LTFU). Twenty-four patients had available SVR12 data; of the patients who did not have these data, 3 were LTFU and 2 died. Baseline demographics and disease characteristics of the 30 patients who received concurrent HCV and MDR-TB treatment are shown in Table 3.

Table 3. Baseline Demographics and Disease Characteristics (Melikyan et al)[5]

Key Demographics and Characteristics	MDR-TB Patients Who Received HCV Treatment (N=30)
Age, median (IQR), years	52 (41–56)
Male, n (%)	29 (96.7)
Incarceration (former/current), n (%)	16 (53.3)
Current alcohol consumption, n (%)	15 (50)
IV drug use (former/current), n (%)	11 (36.7)

Key Demographics and Characteristics			MDR-TB Patients Who Received HCV Treatment (N=30)
HCV GT, 1b/2/3a/4/indeterminate, n (%)			9 (30)/4 (13.3)/15 (50)/1 (3.3)/1 (3.3)
FibroScan results,[a] n (%)	F0–F1		22 (73.3)
	F2		3 (10)
	F3		2 (6.7)
	F4		3 (10)
Antiretroviral therapies, n (%)	EFV + ABC + 3TC		9 (30)
	EFV + NVP		6 (20)
	Tenofovir		5 (16.7)
	LPV/r		2 (6.7)
MDR-TB drugs, n (%)	Group A	Levofloxacin	18 (60)
		Linezolid	16 (53.3)
		Bedaquiline	6 (20)
		Moxifloxacin	5 (16.7)
	Group B	Cycloserine	26 (86.7)
		Clofazimine	19 (63.3)
	Group C	Delamanid	13 (43.4)
		p-aminosalicylic acid	13 (43.3)
		Prothionamide	12 (40)
		Pyrazinamide	8 (26.7)
		Imipenem/cilastatin	6 (20)
		Capreomycin	4 (13.3)
		Kanamycin	4 (13.3)

Abbreviations: 3TC=lamivudine; ABC=abacavir; LPV/r=lopinavir/ritonavir.
[a]F0–F1 was 2.5–7 kPa, F2 was 7.1–9.4 kPa, F3 was 9.5–14.5 kPa, and F4 was >14.5 kPa.

Effectiveness

Overall, of the 30 patients who began HCV treatment, 23 patients (76.7%) achieved SVR12. Of the 24 patients who had HCV PCR testing results at the SVR12 time point, 23 patients (95.8%) achieved SVR12. One patient who was HIV-positive with HCV GT 3a and F0–F1 fibrosis experienced treatment failure after 12 weeks of treatment with SOF + DCV, possibly due to poor adherence. Of the 6 patients who did not have HCV PCR testing results at the SVR12 time point, 4 had HCV PCR data at EOT, and each had negative HCV PCR results.

Safety

Throughout treatment and during the 12 weeks after treatment, 1 patient (3.3%) experienced an SAE that was considered as possibly related to SOF + DCV treatment: 16 days after treatment initiation, the patient experienced a Grade 3 severe allergic reaction that required a temporary interruption in HCV and MDR-TB treatment, and the event resolved with antihistamine treatment. Both treatments were completed successfully. Four AEs of clinical significance that were related to MDR-TB treatment were reported: Grade 2 anemia (n=1), Grade 1 dizziness (n=1), Grade 1 peripheral neuropathy (n=1), and Grade 1 platelet decrease (n=1).

References

1. Enclosed. Gilead Sciences Inc, VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir [SOF/VEL/VOX]) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.

3. Enclosed. Gilead Sciences Inc, HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
4. Enclosed. Gilead Sciences Inc, SOVALDI® (sofosbuvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
5. Melikyan N, Huerga H, Atshemyan H, et al. Concomitant Treatment of Chronic Hepatitis C With Direct-Acting Antivirals and Multidrug-Resistant Tuberculosis Is Effective and Safe. *Open Forum Infect Dis.* 2021;8(2):ofaa653.

Abbreviations

Ab=antibody
AE=adverse event
RBV=ribavirin
DCV=daclatasvir
EFV=efavirenz
EOT=end of treatment
GS-331007=predominant circulating metabolite of SOF
GT=genotype
LDV=ledipasvir
LTFU=lost to follow-up
MDR-TB=multi-drug–resistant tuberculosis
NVP=nevirapine
P-gp=P-glycoprotein
PCR=polymerase chain reaction
PK=pharmacokinetic(s)
QTc=corrected QT
SAE=serious adverse event
SOF=sofosbuvir
SVR12=sustained virologic response 12 weeks after end of treatment
TB=tuberculosis
VEL=velpatasvir
VOX=voxilaprevir

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa, Harvoni, Sovaldi, and Vosevi US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi; www.gilead.com/-/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_pi; www.gilead.com/-/media/files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi; www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.

Follow-Up

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