GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Concomitant Use With Proton Pump Inhibitors at High Doses or With Twice-Daily Dosing

This document is in response to your request for information regarding the concomitant use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) with proton pump inhibitors (PPIs) at high doses or with twice-daily dosing.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/~/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Summary

Product Labeling[1]

Coadministration of omeprazole or other PPIs is not recommended. If it is considered medically necessary to coadminister, SOF/VEL should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other PPIs has not been studied.

Additionally, there is no information in the SOF/VEL product labeling regarding SOF/VEL and PPIs with high-dose and/or twice-daily dosing.

Clinical Data on Concomitant Use of SOF/VEL and High-Dose or Twice-Daily PPIs

A retrospective cohort study found PPI use was not significantly associated with SVR achievement when compared to no PPI use (*P*=0.087). However, a post hoc analysis found that the SVR rate was significantly lower in patients who received either high-dose or twice-daily dosing of PPIs than in the overall study population (*P*=0.001 and *P*<0.0001, respectively).[2]

A retrospective analysis of data from DHC-R evaluated effectiveness of SOF/VEL ± RBV administered with or without PPIs. Overall, rates of SVR12 were high regardless of concomitant PPI use: without concomitant PPI, 98%; with concomitant PPI, 96%. No impact on the achievement of SVR12 was observed among patients who received doses of PPIs >20 mg.[3]

Clinical Data on Concomitant Use of SOF/VEL and High-Dose or Twice-Daily PPIs

Retrospective Cohort Study[2]

Study design and demographics

A retrospective cohort study from 128 Veterans Affairs Medical Centers across the US evaluated the impact of PPI use in patients who were concomitantly treated with SOF/VEL. Patients were included in the analysis if they received a full course of SOF/VEL (defined as 77–91 days SOF/VEL therapy received within an 84-day period [SD, ±7 days]) and had HCV RNA laboratory results within an appropriate timeframe after completion of treatment. Patients were excluded if their race, baseline cirrhosis status, or HCV GT was unknown and if another direct-acting antiviral was previously utilized for HCV treatment. This study did not differentiate between virologic failure or relapse and HCV re-infection.

The primary endpoint was SVR, defined as undetectable HCV RNA ≥10 weeks after SOF/VEL treatment completion. A post hoc analysis was conducted and included the following variables to describe PPI exposure: PPI prescription (yes or no); the PPI drug administered; dose frequency (once, twice, or three times daily); and low-dose (20 mg omeprazole daily or equivalent) or high-dose PPI (>20 mg omeprazole equivalents daily).

Table 1. Baseline Demographics and Disease Characteristics (Rumph et al)[2]

Key Demographics and Characteristics		Without Concomitant PPI (n=3178)	With Concomitant PPI (n=830)	*P*-Value
Age, median (IQR), years		62 (58–66)	63 (59–67)	0.0007
Male, n (%)		3040 (95.7)	807 (97.2)	0.04
African American, n (%)		440 (13.9)	107 (12.9)	0.48
Cirrhosis,[a] n (%)		687 (21.6)	215 (25.9)	0.008
GT, n (%)	1a/1b	153 (4.8)/23 (0.7)	48 (5.8)/9 (1.1)	0.103
	2	1737 (54.7)	469 (56.5)	
	3	1176 (37)	273 (32.9)	
	4, 5, 6, or mixed	89 (2.8)	31 (3.7)	

[a]Defined as a Fibrosis-4 score >3.25.

Results

Of the 4008 patients included in the analysis, 97.7% achieved SVR. The SVR rate for patients with or without concomitant PPI use was 96.7% and 97.9%, respectively (*P*=0.045).

When adjusted for other variables using a full logistic model, PPI use was not significantly associated with a decreased SVR achievement (OR, 0.67; *P*=0.087). According to the adjusted model, the only independent variables that had a statistically significant effect on SVR were a BMI >30 kg/m^2 (OR, 0.52; *P*=0.002) and the presence of cirrhosis (OR, 0.48; *P*=0.001).

The post hoc analysis demonstrated that the SVR rate was significantly lower in patients who received either high-dose (94%) or twice-daily dosing (92%) of PPIs than in the overall study population (97.7%; *P*=0.001 and *P*<0.0001, respectively).

Table 2. Post Hoc Analysis of the Effect of PPI Exposure on SVR (Rumph et al)[2]

Category		n	SVR, n	SVR % (95% CI)	*P*-Value[a]	Adjusted *P*-Value[b]
Total sample		4008	3915	97.7 (–)	–	–
PPI use	No	3178	3112	97.9 (97.4–98.4)	0.4	1
	Yes	830	803	96.7 (95.3–97.7)	0.067	0.4
Name of PPI	Omeprazole	703	682	97 (95.5–98)	0.22	1
	Pantoprazole	125	120	96 (91–98.3)	0.2	1
	Lansoprazole[c]	1	1	–	–	–
	Esomeprazole[c]	1	0	–	–	–
Dosing frequency of PPI	Once daily	667	653	97.9 (96.5–98.7)	0.73	1
	Twice daily	162	149	92 (86.8–95.3)	<0.0001	<0.0001
	Three times daily[c]	1	1	–	–	–
PPI dose category	Low dose	598	585	97.8 (96.3–98.7)	0.84	1
	High dose	232	218	94 (90.1–96.4)	0.0001	0.001

[a]The unadjusted *P*-value is associated with probability that the category SVR was equal to the SVR probability for the overall study population (3915 out of 4008; 97.7%).
[b]Holm-adjusted *P*-value for multiple testing.
[c]Not tested for statistical significance.

DHC-R Retrospective Cohort Study[3]

Study design and demographics

A retrospective analysis of data from DHC-R, an ongoing noninterventional, prospective, multicenter registry, evaluated the effectiveness of SOF/VEL ± RBV administered with or without PPIs. Eligible patients were treatment naive, had received SOF/VEL ± RBV between July 2016 and March 2022 (N=1154), and received concomitant PPIs (n=98; 8.5%) or no PPIs (n=1056; 91.5%). SVR12 was assessed in the effectiveness populations, which was defined as patients from the mITT population with SVR12 data and excluded patients with missing data and those who discontinued treatment, had nonresponse at end of treatment, or had confirmed/possible reinfections. The most frequently used PPI was pantoprazole (n=78); 19 patients also received omeprazole, and 1 received esomeprazole.

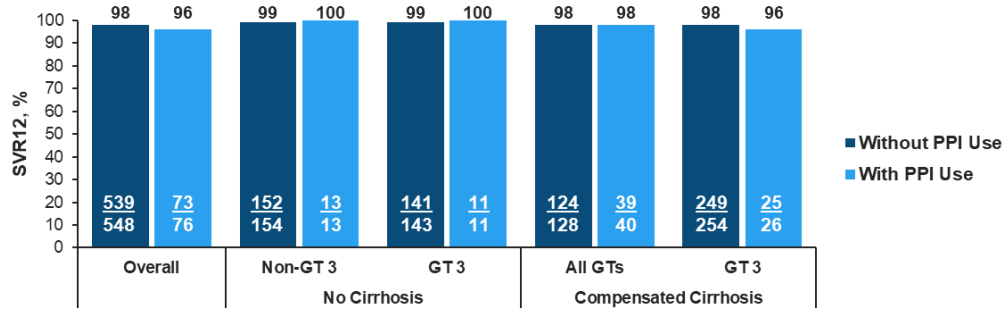
Table 3. DHC-R: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics	Without Concomitant PPI (n=1056)	With Concomitant PPI (n=98)
Age, median, years	47	53
<35 years, %	11	5
35–50 years, %	52	36
50–65 years, %	32	42
>65 years, %	5	17
Male, %	73	62
HCV GT 3, %	62	47
Compensated cirrhosis, %	32	50
Decompensated cirrhosis, %	4	17

Results

Rates of SVR12 were high regardless of concomitant PPI use (without concomitant PPI, 98%; with concomitant PPI, 96%) and across subgroups (Figure 1). Notably, 9 patients received PPIs in addition to metamizole, another medication with a drug-drug interaction; all of these patients (100%) achieved SVR12.

Figure 1. DHC-R: Rates of SVR12 Overall and by GT and Cirrhosis Status (Effectiveness Population)[3]



Although the subgroup of patients who received PPI doses >20 mg was small, no impact on the achievement of SVR12 was observed (Table 4). Three virologic relapses occurred in subgroups of patients that received higher PPI doses and whose baseline characteristics were classified as harder to treat: pantoprazole 40 mg with GT 3 and decompensated cirrhosis, n=2, and pantoprazole 20 mg with GT 3 and compensated cirrhosis, n=1.

Table 4. DHC-R: Effectiveness of SOF/VEL ± RBV With Different PPI Doses[3]

PPI Dose	n[a]	% of PPI-Treated Patients	Total SVR12 mITT,[a] %	Total Relapses, n
20 mg	42; pantoprazole, n=28; omeprazole, n=14	43	97	1
40 mg	31; pantoprazole, n=29; omeprazole, n=2	32	92	2
80 mg	3; pantoprazole, n=2; esomeprazole, n=1	3	100	0
Unknown	22; pantoprazole, n=19; omeprazole, n=3	22	100	0
Total	98	100	96	3

[a]Effectiveness population mITT outcomes by dose: 20 mg, 36/37 (97%) and 1 relapse; 40 mg, 22/24 (92%) and 2 relapses; 80 mg, 2/2 (100%) and no relapses; and unknown dose, 13/13 (100%) and no relapses.

No safety data were reported.

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Rumph DM, Straley CM, Kolberg JL, Jacob DA. Impact of proton pump inhibitors on sustained virologic response in veterans treated with sofosbuvir/velpatasvir for chronic hepatitis C virus: A retrospective cohort study. *Pharmacotherapy.* 2022;42(5):397-404.
3. Cornberg M, Stoehr A, Teuber G, et al. HepatitisUse of proton pump inhibitors among German Hepatitis C patients treated withs ofosbuvir/velpatasvir: Data from the German Hepatitis C-Registry (2016 -2022) [Poster #THU-366]. Paper presented at: European Association for the Study of the Liver (EASL); June 5-8, 2024; Milan, Italy.

Abbreviations

DHC-R=Deutsches Hepatitis C-Register
GT=genotype
mITT=modified ITT
OR=odds ratio
PPI=proton pump inhibitor
RBV=ribavirin
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=sustained virologic response 12 weeks after end of treatment
VEL=velpatasvir

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: www.gilead.com/~/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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