GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Coadministration With Proton Pump Inhibitors

This document is in response to your request for information regarding the coadministration of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) with proton pump inhibitors (PPIs).

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 SOF/VEL with 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.

Clinical and RWD on SOF/VEL Coadministration With PPIs

A retrospective analysis of 12 RCTs and RWD assessed the relationship between SVR12 and PPI use in patients receiving SOF/VEL ± PPI (N=5769). The overall SVR12 rates in each group were comparable with and without use of PPIs, with 97% of the RCT group and 99% of the RWD group achieving SVR12.[2]

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).[3]

A large, real-world cohort study evaluated the use of SOF/VEL ± RBV, including patients with concomitant PPI use. The SVR12 rate in patients who were receiving concomitant PPIs (n=354) was 95.5%, which was not significantly different than the 97.8% rate reported in patients who were not receiving PPIs (n=622; *P*=0.48).[4]

Clinical and RWD on SOF/VEL Coadministration With PPIs

Pooled Analysis of RCTs and RWD

Study design and demographics

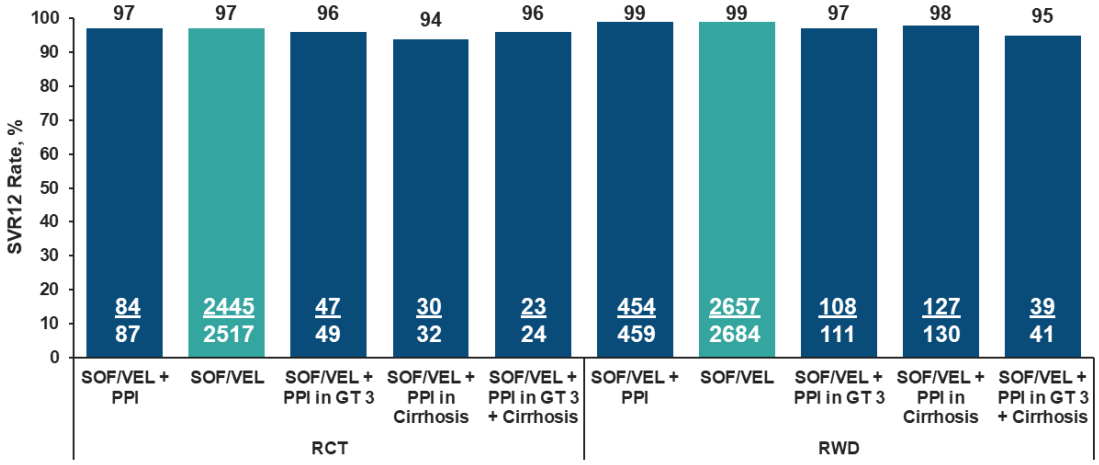
A retrospective pooled analysis that included 12 phase 2/3 clinical trials across North America, Europe, Asia, and Australia and RWD from 12 clinical practice cohorts across North America and Europe was conducted to assess the clinical relationship between SVR12 and PPI use in patients treated with 12 weeks of SOF/VEL for HCV. The main outcome measures included the rates of both SVR12 and relapse among patients receiving SOF/VEL ± PPI.[2]

The baseline demographics and disease characteristics among PPI users in the RCT population (n=87) were the following: mean (range) age, 57 (26–78) years; male, n=69 (79%); cirrhosis, n=32 (37%); and HCV GT 3, n=49 (56%). Those among PPI users in the RWD population (n=481) were the following: mean (range) age, 63 (25–90); male, n=258 (54%); cirrhosis, n=141 (29%); and HCV GT 3, n=118 (25%).[2]

Results[2]

Sixty-six percent of PPI-using patients (57/87) enrolled in the RCTs received PPIs during the 12-week duration of SOF/VEL treatment; 68% of those who used a PPI used omeprazole. The overall SVR12 rates in each group were comparable with and without PPIs, with 97% of the RCT group and 99% of the RWD group achieving SVR12 (Figure 1).

Figure 1. SVR12 Rates by RCT and RWD Populations (Buti et al)[2]



Among patients receiving SOF/VEL + PPI, 3 patients did not achieve SVR12; 2 patients relapsed, and 1 patient with a history of diabetes discontinued SOF/VEL after 7 days of treatment due to hyperglycemia.

Safety data were not reported.

Retrospective Study on SOF/VEL With High-Dose or Twice-Daily PPIs[3]

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 virological failure or relapse vs 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)[3]

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

[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 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 (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)[3]

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
PPI use - yes	830	803 (96.7)	95.3–97.7	0.067	0.4
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	–	–	–
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	–	–	–
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 entire cohort (3915/4008; 97.7%).
[b]Holm-adjusted *P*-value for multiple testing.
[c]Not tested for statistical significance.

Italian Real-World Cohort[4]

Study design and demographics

A large Italian, real-world cohort evaluated the safety and effectiveness of 12 weeks of treatment with SOF/VEL ± RBV in 1429 patients who had data in the Puglia registry between June 2017 and May 2018. At the time of analysis, 1319 patients (92%) had reached the 12-week post-treatment assessment time point and had the following baseline demographics and disease characteristics: mean age, 64 years; male, 59%; treatment naïve, 80%; fibrosis stages, F0–1/2/3/4, 25%/30%/23%/21%; HCV GT 1/2/3/4/5/6, 42%/39%/15%/3%/0%/<1%; and mean Fibrosis-4 score, 3.05. Fifty-three percent of patients (n=697) were receiving PPIs at baseline.

Efficacy

The overall ITT SVR12 rate was 99% (1299/1319). Of the 697 patients who were on PPIs at baseline, 354 (51%) continued treatment and achieved SVR12 at a rate of 95.5%; the SVR12 rate among those who did not use PPI at baseline was 97.8% (*P*=0.48).

Of patients in the overall study population who did not achieve SVR12 (n=20), 8 patients relapsed (2 of whom were reinfected), 7 patients discontinued treatment early, and 5 patients were lost to follow-up.

Safety

Any-grade AEs were experienced by 76% of patients (n=969) in the SOF/VEL group and 73% of patients (n=30) in the SOF/VEL + RBV group. AEs that occurred in ≥5% of patients in the SOF/VEL and SOF/VEL + RBV groups were fatigue (n=907 [71%] and n=36 [88%], respectively), headache (n=881 [69%] and n=34 [83%]), nausea (n=830 [65%] and n=24 [59%]), anemia (n=5 [<1%] and n=13 [32%]), and diarrhea (n=40 [3%] and n=11 [27%]). SAEs were experienced by 1% of patients (n=18) in the SOF/VEL group and 2% of patients (n=1) in the SOF/VEL + RBV group. No SAEs were deemed related to treatment in either group, and no AEs led to treatment discontinuation.

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Buti M, Esteban R, Flamm S, et al. Concomitant use of Proton Pump Inhibitors and Sofosbuvir/Velpatasvir: Evidence from Randomized Clinical Trials and Real-World Data [Poster #THU-219]. Paper presented at: European Association for the Study of the Liver Congress; June, 21-24, 2023; Vienna, Austria.
3. 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.
4. Mangia A, Piazzolla V, Giannelli A, et al. SVR12 Rates Higher Than 99% After Sofosbuvir/Velpatasvir Combination in HCV Infected Patients with F0-F1 Fibrosis Stage: A Real World Experience. *PLoS ONE.* 2019;14(5):e0215783. https://www.ncbi.nlm.nih.gov/pubmed/31091254

Abbreviations

AE=adverse event
GT=genotype
OR=odds ratio
PPI=proton pump inhibitor
RBV=ribavirin
RCT=randomized controlled trial
RWD=real-world data
SAE=serious adverse event
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

Adverse Event Reporting

Please report all adverse events to:

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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