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Epclusa® (sofosbuvir/velpatasvir) Use Without Ribavirin in Decompensated Cirrhosis

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) without ribavirin (RBV) in patients with HCV infection and decompensated cirrhosis.

This response was developed according to principles of evidence-based medicine and only contains data from meta-analyses and clinical studies (N≥100).

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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]

SOF/VEL is indicated for the treatment of adults and pediatric patients ≥3 years of age with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, or with decompensated cirrhosis for use in combination with RBV. The recommended treatment duration of SOF/VEL ± RBV is 12 weeks.

Clinical Data on SOF/VEL Use Without RBV in Decompensated Cirrhosis

In a systematic review and meta-analysis that compared the efficacy and safety of SOF/VEL for 12 weeks (n=481) with SOF/VEL + RBV for 12 to 24 weeks (n=391).[2]

- The pooled SVR12 rate in patients treated with SOF/VEL with or without RBV (N=872) was 95%. SOF/VEL + RBV did not significantly improve SVR rates compared with SOF/VEL alone (95% vs. 94%; *P*=0.92).
- SOF/VEL + RBV for 12 weeks did not significantly reduce virologic relapse rates compared with SOF/VEL alone (1% [n/N=2/158; 95% CI: 0–8] vs. 6% [n/N=12/197; 95% CI: 3–10]; *P*=0.15).
- Compared with SOF/VEL alone, SOF/VEL + RBV for 12 weeks was associated with significantly higher rates of AEs (47% vs 92%; *P*<0.01), severe AEs (7% vs 24%; *P*=0.02), treatment discontinuation (1% vs 3%; *P*=0.05), and death (2% vs 7%; *P*=0.05). SOF/VEL + RBV was also associated with significantly higher rates of RBV-related toxicities.

In the phase 3 ASTRAL-4 study of SOF/VEL in TN and TE participants with decompensated cirrhosis and HCV GTs 1 through 6, participants were randomly assigned in a 1:1:1 ratio to receive SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, or SOF/VEL for 24 weeks.[3]

- In a post hoc analysis, there were no significant differences in SVR12 rates between the treatment groups: SOF/VEL for 12 weeks, 83%; SOF/VEL for 24 weeks, 86%; SOF/VEL + RBV for 12 weeks, 94% (each, *P*>0.05; significance level set at 0.0167).[3,4]
- The most common AEs (≥10%) that occurred in the SOF/VEL for 24 weeks group were fatigue (23%), nausea (20%), headache (19%), and insomnia (10%).[3]

In a multicenter study of SOF/VEL treatment in Japanese participants with decompensated cirrhosis, the SVR rate was 91.3% (188/206). Improvement in liver function was observed, as indicated by an increased proportion of participants with CP Class A at Week 24 after EOT, followed by a gradual decline through Year 5. Liver transplant–free survival rates at Years 1, 3, and 5 were 94%, 82.9%, and 69%, respectively. Overall, 43 participants died, and 4 underwent liver transplantation; causes of death included liver failure, non–liver-related conditions, HCC, and variceal rupture.[5]

Clinical Data on SOF/VEL Use Without RBV in Decompensated Cirrhosis

Systematic Review and Meta-analysis[2]

Study design

A systematic review and meta-analysis of 13 studies in patients with HCV-associated decompensated cirrhosis (N=872), including two randomized controlled trials, five prospective cohort studies, and six retrospective studies published through September 2024, compared the efficacy and safety of SOF/VEL for 12 weeks (n=481) with those of SOF/VEL + RBV for 12 to 24 weeks (n=391). The primary efficacy endpoint was SVR12. Secondary endpoints included virologic relapse, AEs, severe AEs, and discontinuation rates.

Efficacy

The pooled SVR12 rate in patients treated with SOF/VEL with or without RBV was 95% (n/N=808/872; 95% CI: 92–97). SOF/VEL + RBV did not significantly improve SVR rates compared with SOF/VEL alone (95% [n/N=366/391; 95% CI: 89–99] vs. 94% (n/N=442/481; 95% CI: 90–97]; *P*=0.92). In a subgroup analysis, SVR12 rates were not significantly different between patients receiving SOF/VEL + RBV for 12 weeks compared with those receiving SOF/VEL for 24 weeks (95% [n/N=366/391; 95% CI: 89–99] vs. 88% [n/N=117/133; 95% CI: 82–93]; *P*=0.23).

SOF/VEL + RBV for 12 weeks did not significantly reduce virologic relapse rates compared with SOF/VEL alone (1% [n/N=2/158; 95% CI: 0–8] vs. 6% [n/N=12/197; 95% CI: 3–10]; *P*=0.15).

Subgroup analysis by GT

SOF/VEL + RBV did not significantly increase the SVR12 rate in patients with GTs 1, 2, or 4; however, SOF/VEL + RBV significantly increased the SVR12 rate for patients with GT 3 (Table 1). In addition, SOF/VEL + RBV significantly decreased virologic relapse rates in patients with GT 3 compared with no significant decrease observed in patients with non-GT 3.

Table 1. SVR12 and Virologic Relapse by GT (Xiao et al)[2]

Subgroup	SOF/VEL		SOF/VEL + RBV		*P*-value
	n/N	% (95% CI)	n/N	% (95% CI)	
SVR12					
GT1	141/155	91 (86–95)	156/172	90 (82–97)	0.95
GT2	29/31	95 (82–100)	57/63	94 (85–100)	0.86
GT4[a]	2/2	100 (16–100)	4/4	100 (40–100)	0.85
Non-GT3	174/190	92 (87–95)	220/243	90 (82–96)	0.86
GT3	7/15	45 (13–79)	26/30	87 (71–98)	<0.01
Virologic relapse					
GT3[a]	1/1	100 (2–100)	0/10	0 (0–31)	0.02
Non-GT3	7/114	6 (2–12)	2/158	1 (0–8)	0.16

[a]Outcomes should be interpreted with caution because of the small sample sizes in the treatment groups.

Safety

Significantly more of the patients treated with SOF/VEL + RBV for 12 weeks than of those treated with SOF/VEL alone experienced AEs (92% [n/N=261/287; 95% CI: 88–95] vs. 47% [n/N=167/348; 95% CI: 24–71]; *P*<0.01). The most commonly reported AEs were fatigue, headache, nausea, and malaise; incidence rates were not reported.

Pooled estimates for each common AE found that significantly more of the patients treated with SOF/VEL + RBV than of those treated with SOF/VEL alone experienced AEs known to be associated with RBV (Table 2). In addition, significantly more of the patients treated with SOF/VEL + RBV for 12 weeks than of those treated with SOF/VEL alone for 12 weeks experienced severe AEs (24% [n/N=64/287; 95% CI: 12–38] vs. 7% [n/N=32/348; 95% CI: 2–15]; *P*=0.02).

Table 2. Pooled Incidence of AEs With SOF/VEL + RBV vs SOF/VEL (Xiao et al)[2]

AEs		SOF/VEL		SOF/VEL + RBV		*P*-value
		n/N	% (95% CI)	n/N	% (95% CI)	
Fatigue		32/225	11 (1–29)	129/204	64 (35–89)	<0.01
Hyperbilirubinemia		9/258	3 (0–8)	23/83	28 (18–39)	<0.01
Anemia	Moderate[a]	9/141	6 (3–11)	60/255	23 (16–31)	<0.01
	Severe[b]	1/90	1 (0–6)	15/204	6 (3–10)	0.02
Malaise		2/72	3 (0–10)	6/32	19 (7–36)	<0.01
Hyperkalemia		6/141	2 (0–13)	41/245	17 (12–22)	0.02
Dyspnea		5/162	3 (1–6)	20/194	10 (6–15)	<0.01
Cough		2/90	2 (0–8)	9/87	10 (5–19)	0.02

[a]Defined as reduced Hgb level <10 g/dL.
[b]Defined as severe reduced Hgb level <8.5 g/dL.

Significantly more of the patients treated with SOF/VEL + RBV for 12 weeks than of those treated with SOF/VEL alone discontinued treatment (3% [n/N=12/287; 95% CI: 1–6] vs. 1% [n/N=8/430; 95% CI: 0–3]; *P*=0.05). In addition, significantly more of the patients treated with SOF/VEL + RBV for 12 weeks than of those treated with SOF/VEL alone died (7% [n/N=20/287; 95% CI: 2–16] vs. 2% [n/N=8/366; 95% CI: 1–4]; *P*=0.05).

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ASTRAL-4: SOF/VEL ± RBV for 12 or 24 Weeks[3]

Study design and demographics

ASTRAL-4 was a phase 3, open-label study in TN and TE participants with HCV GTs 1 through 6 with decompensated cirrhosis (CPT Class B). Participants were randomly assigned in a 1:1:1 ratio to receive SOF/VEL daily for 12 weeks, SOF/VEL + RBV for 12 weeks, or SOF/VEL for 24 weeks.

Of the 267 participants enrolled, 78% were GT 1, 4% were GT 2, 15% were GT 3, 3% were GT 4, and <1% were GT 6. Most participants (95%) had a baseline MELD score ≤15, and 55% were TE. Although all participants had CPT Class B cirrhosis at screening, 27 participants had CPT Class A or C cirrhosis at treatment initiation.

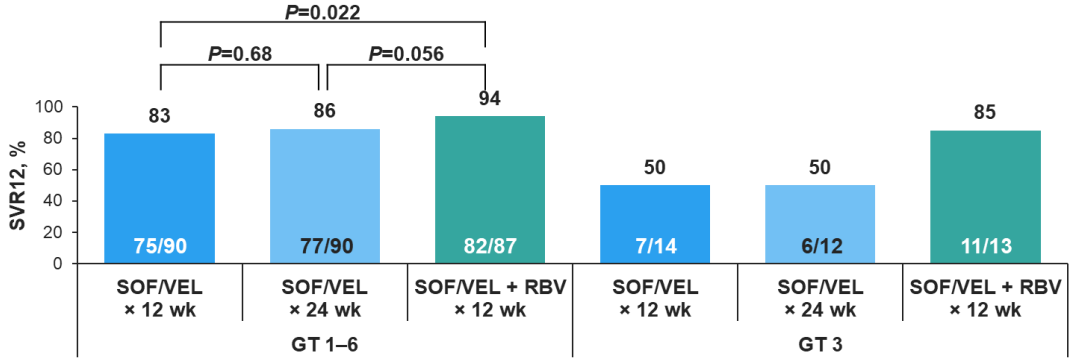
Table 3. ASTRAL-4: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics		SOF/VEL		SOF/VEL + RBV × 12 Weeks (n=87)
		12 Weeks (n=90)	24 Weeks (n=90)	
Age, mean (range), years		58 (42–73)	58 (46–72)	58 (40–71)
Male, n (%)		57 (63)	63 (70)	66 (76)
Race, n (%)	White	79 (88)	81 (90)	79 (91)
	Black	6 (7)	6 (7)	5 (6)
	Asian	3 (3)	2 (2)	0
	Other	2 (2)	1 (1)	3 (3)
HCV RNA	Mean (SD), $\log_{10}$ IU/mL	6 (0.5)	5.9 (0.6)	5.8 (0.6)
	≥800,000 IU/mL, n (%)	59 (66)	45 (50)	45 (52)
HCV GT, 1a/1b/2/3/4/6, %		56/20/4/16/4/0	61/18/4/13/2/1	62/16/5/15/2/0
CPT score, ≤6/7/8/9/10, %		3/40/34/21/1	8/23/38/24/7	7/26/47/15/5
MELD score, n (%)	<10	36 (40)	26 (29)	29 (33)
	10–15	50 (56)	59 (66)	54 (62)
	≥16	4 (4)	5 (6)	4 (5)
eGFR, mean (range), mL/min		89 (15–169)	90 (43–198)	90 (50–167)

Efficacy

SVR12 rates for each of the three treatment groups are shown in Figure 1. In a post hoc analysis, there were no significant differences in SVR12 rates among the three treatment groups (Figure 1). A total of 22 participants experienced virologic failure (Figure 2), and 20 of those participants experienced relapse. Two participants with GT 3 experienced virologic breakthrough.

Figure 1. ASTRAL-4: SVR12 Rates Overall and in Participants With GT 3[3,4]

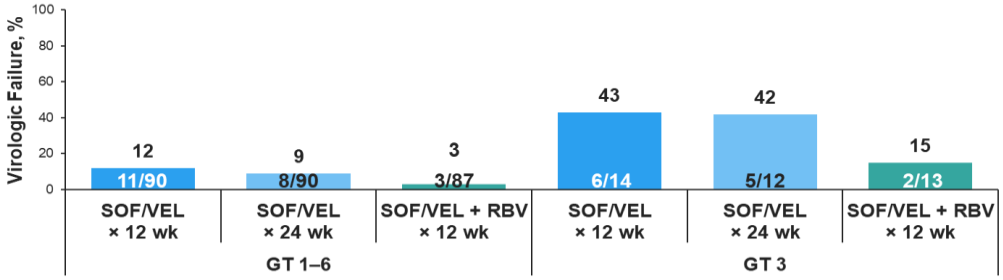


Note: *P*-values were calculated for a post hoc analysis; however, the study was not adequately powered to determine differences between treatment groups.

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Figure 2. ASTRAL-4: Virologic Failure Rates Overall and in Participants With GT 3[3]



Safety

Overall safety outcomes by treatment group are presented in Table 4. Decreases in Hgb, lymphocytes, and platelets were observed in all three treatment groups.

Table 4. ASTRAL-4: Safety Outcomes[3]

Safety Outcomes, n (%)		SOF/VEL		SOF/VEL + RBV × 12 Weeks (n=87)
		12 Weeks (n=90)	24 Weeks (n=90)	
Serious AEs		17 (19)	16 (18)	14 (16)
Discontinuations due to AEs		1 (1)	4 (4)	4 (5)
Deaths[a]		3 (3)	3 (3)	3 (3)
Common AEs (>10% of participants in any group)	Fatigue	23 (26)	21 (23)	34 (39)
	Headache	23 (26)	17 (19)	18 (21)
	Nausea	22 (24)	18 (20)	22 (25)
	Pruritus	10 (11)	4 (4)	4 (5)
	Insomnia	9 (10)	9 (10)	12 (14)
	Diarrhea	6 (7)	7 (8)	18 (21)
	Anemia	4 (4)	3 (3)	27 (31)
	Dyspnea	4 (4)	2 (2)	9 (10)
	Muscle spasm	3 (3)	4 (4)	10 (11)
	Cough	2 (2)	0	9 (10)
Reduced Hgb level	<10 g/dL	7 (8)	8 (9)	20 (23)
	<8.5 g/dL	1 (1)	1 (1)	6 (7)
Reduced lymphocyte count	350 to <500/mm^3	10 (11)	8 (9)	12 (14)
	<350/mm^3	3 (3)	6 (7)	12 (14)
Reduced platelet count	25,000 to <50,000/mm^3	15 (17)	18 (20)	10 (11)
	<25,000/mm^3	1 (1)	0	0

[a]Two participants died <30 days after they discontinued study treatment, and 7 participants died >30 days after the end of treatment; all deaths were deemed unrelated to study treatment. Most of the deaths were due to complications of end-stage liver disease (ie, liver failure, sepsis, or multiorgan failure).

Long-Term Outcomes in SOF/VEL-Treated Japanese Participants With Decompensated Cirrhosis[5]

Study design and demographics

A multicenter study evaluated changes in liver function and liver transplant–free survival following treatment with SOF/VEL in Japanese participants with decompensated cirrhosis, defined as CP Class B or C at enrollment or CP Class A with prior decompensation. A total of 206 participants who received 12 weeks of SOF/VEL between February 2019 and December 2021 were enrolled. Clinical and laboratory data were collected at baseline, EOT, Weeks 12 and 24 after EOT, and every 6 months thereafter. Changes in liver function were evaluated based on the proportion of participants with CP Class A. For the survival analysis,

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the observation period began on the date of SOF/VEL initiation and ended at the earliest of death, liver transplantation, or last hospital visit.

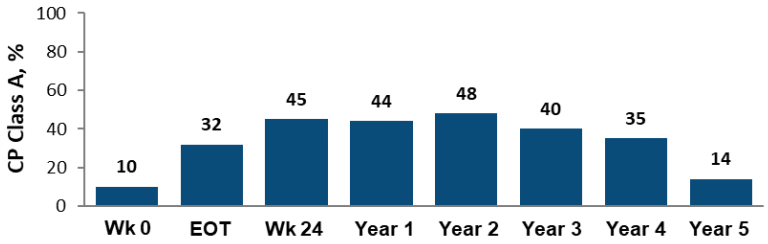
Table 5. Baseline Demographics and Disease Characteristics (Tahata et al)[5]

Key Demographics and Characteristics	SOF/VEL (N=206)
GT, 1/2/3/4/1 + 2/unknown, n	131/71/1/0/1/2
HCV RNA, median (IQR), log IU/mL	5.7 (5.1–6.1)
CP Class, A/B/C, n	20/156/30
MELD score, median (IQR)	11 (9–12)
History of HCC, n (%)	82 (40)
Esophageal gastric varix, absent/F1/F2 or more/history of varix rupture, n	46/74/41/17
Ascites, Grade 1/2/3, n	72/110/24
Encephalopathy, Grade 1/2/3, n	173/33/0
AFP level, median (IQR), ng/mL	8.6 (4.4–20.3)

Efficacy

Overall, 91.3% of participants (188/206) achieved SVR in the ITT analysis. Seven participants experienced virologic failure, 2 had missing HCV RNA data, 4 were lost to follow-up, and 5 died prior to SVR confirmation. The proportion of participants who changed to CP Class A increased at Week 24 after EOT, followed by a gradual decline through Year 5 after EOT (Figure 3).

Figure 3. Changes in the Proportion of Participants With CP Class A Through Year 5 After EOT (Tahata et al)[5]



Over the 43.7-month period following SOF/VEL initiation, 43 participants died, and 4 underwent liver transplantation. Causes of death included liver failure (n=19), non–liver-related conditions (n=13), HCC (n=10), and variceal rupture (n=1). The 1-year, 3-year, and 5-year liver transplant–free survival rates were 94%, 82.9%, and 69%, respectively. Liver transplant–free survival rates by virologic outcomes and CP class at 12 weeks after the EOT are presented in Table 6.

Table 6. Liver Transplant–free Survival Rates by Virologic Outcomes and CP Class at 12 Weeks After the EOT (Tahata et al)[5]

Virologic Outcomes and CP Class at 12 Weeks After EOT, n/N or %	Events[a]	Year 1	Year 3
Virologic failure	3/7	100	50
SVR	38/188	96.2	86.3
CP Class A[b]	6/76	100	91.9
CP Class B[c]	25/97	95.8	86.4
CP Class C	10/18	81.6	46

[a]Died or underwent liver transplantation.
[b]*P*=0.012 vs CP Class B; *P*<0.001 vs CP Class C.
[c]*P*<0.001 vs CP Class C.

Factors associated with liver transplant–free survival were analyzed, excluding 11 participants with non-evaluable SVR data. In the multivariate analysis, virologic response and CP Class B and C at 12 weeks after the EOT were identified as significant factors (*P*=0.04, *P*=0.015, and *P*<0.001, respectively).

References

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3. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. *N Engl J Med.* 2015;373(27):2618-2628.
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5. Tahata Y, Hikita H, Mochida S, et al. Long-term prognosis and changes in liver function after direct-acting antiviral treatment in decompensated cirrhotic patients with hepatitis C virus [Poster THU-239]. Paper presented at: European Association for the Study of the Liver Congress; 7-10 May, 2025; Amsterdam, the Netherlads.

Abbreviations

AE=adverse event
AFP=α-fetoprotein
CP=Child-Pugh
CPT=Child-Pugh-Turcotte
EOT=end of treatment
GT=genotype
HCC=hepatocellular carcinoma
MELD=Model for End-Stage Liver Disease
RBV=ribavirin
SOF=sofosbuvir
SVR=sustained virologic response
SVR12=sustained virologic response 12 weeks after end of treatment
TE=treatment-experienced
TN=treatment-naive
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:

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