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Epclusa® (SOF/VEL) Use in Patients With Renal Impairment

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) in patients with renal impairment (eGFR <90 mL/min/1.73 m^2), including those who require hemodialysis (HD).

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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]

No dosage adjustment of SOF/VEL is recommended for patients with mild, moderate, or severe renal impairment, including ESRD requiring dialysis. No safety data are available in patients with both decompensated cirrhosis and severe renal impairment, including ESRD requiring dialysis. Additionally, no safety data are available in pediatric patients with renal impairment. Refer to RBV tablet prescribing information regarding use of RBV in patients with renal impairment.

Clinical Studies of SOF/VEL Use in Participants With Renal Impairment

A systematic review and meta-analysis of 21 studies evaluated SOF-based treatments in 717 patients with Stage 4 or 5 CKD. SVR12/24 was achieved by 97.1% of patients. Of the four studies that reported changes in kidney function, eGFR values were generally unchanged during treatment, and 2 patients discontinued HD as a result of eGFR improvement.[2]

In a phase 2 study that evaluated participants with severe renal impairment, including those undergoing HD (n=54) or PD (n=5), the SVR12 rate was 95%. AEs included headache, fatigue, nausea, vomiting, insomnia, and anemia.[3]

Real-World Studies of SOF/VEL Use in Patients With Renal Impairment

A claims database study in patients with CKD found no difference in the risk of ESRD or dialysis between those treated with SOF-based (n=2042) vs non-SOF-based (n=431) regimens.[4]

In a prospective real-world study, 99.2% of patients (870/877) achieved SVR12 with SOF/VEL ± RBV, and rates were similar (99.1–100%) among subgroups according to baseline eGFR. Patients with baseline eGFR ≤60 mL/min/1.73 m^2 experienced significant increases in eGFR at EOT and SVR12 assessment, whereas those with baseline eGFR >60 mL/min/1.73 m^2 experienced significant decreases in eGFR at both time points.[5]

In retrospective real-world studies conducted in patients with CKD, including those with severe renal impairment, approximately 95% to 100% of those treated with SOF/VEL ± RBV achieved SVR12. Changes in renal laboratory parameters are summarized below.[6,7]

Clinical Studies of SOF/VEL Use in Participants With Renal Impairment

Systematic Review and Meta-Analysis[2]

Study design and demographics

A systematic review and meta-analysis of 21 studies included 717 patients with HCV and Stage 4 or 5 CKD who were treated with SOF-based regimens. Most studies included patients with a history of cirrhosis, and 4 studies included those with decompensated cirrhosis. The following SOF-based regimens were included: SOF + SMV ± RBV, SOF + PEG-IFN, SOF + RBV, SOF + DCV ± RBV, and LDV/SOF ± RBV. The dosing of SOF varied by study: SOF 400 mg once daily, 200 mg once daily, 400 mg every other day, and 400 mg three times weekly. Treatment was administered for 8, 12, 16, or 24 weeks (where reported). Included patients had a mean/median age of 35 to 62 years, and 58% were receiving HD or PD; in 18 studies, the percentages of patients with HCV GTs 1, 2, and 3 were 67%, 8%, and 20%, respectively.

Results

Overall, SVR12/24 was 97.1% (95% CI: 93.9–99.3%; I^2=61%). SVR12/24 rates were significantly higher among the 10 studies that did not utilize RBV in addition to an SOF-based regimen than among those that included RBV in the treatment regimen (99% vs 94%; *P*=0.035). Seven studies included data that allowed comparisons of efficacy outcomes between patients with and those without cirrhosis. Patients without cirrhosis tended to have higher SVR12/24 rates than those with cirrhosis, although the difference was not significant (relative risk, 0.93; 95% CI: 0.85–1.02; I^2=33%).

The pooled SAE rate for the 16 studies with available data was 4.8% (95% CI: 2.1–10.3%; I^2=60%). There was no significant difference in the incidence of SAEs among patients who received full-dose and decreased-dose SOF (8.8% vs 2.9%; *P*=0.13). Of the four studies that reported changes in kidney function, eGFR values were generally unchanged during treatment, and 2 patients discontinued HD as a result of eGFR improvement.

Study 4062: SOF/VEL in Participants Undergoing HD or PD[3]

Study design and demographics

Study 4062 was a phase 2, multicenter, open-label study that evaluated the efficacy and safety of SOF/VEL in 59 participants who were undergoing HD (n=54) or PD (n=5). Participants received SOF/VEL (400/100 mg) daily for 12 weeks, and SVR12 was assessed at Week 24. Pharmacokinetic levels were collected at each study visit while participants were receiving SOF/VEL. At baseline, the mean age was 60 years, 59% (35/59) were males, 29% (17/59) had compensated cirrhosis, and 22% (13/59) were treatment experienced. The mean duration of dialysis was 7.3 years, and 32% (19/59) had a history of kidney transplant.

Results

SVR12 was achieved in 95% of participants (56/59). Among the 3 participants who did not achieve SVR12, 1 participant with HCV GT 3 and cirrhosis relapsed, 1 discontinued the study due to low study drug adherence and subsequently relapsed, and 1 achieved SVR4 and died by suicide after the 12-week study period.

The most common (≥10%) AEs were headache (17%), fatigue (14%), nausea (14%), vomiting (14%), and insomnia (10%). Seven Grade 3 AEs and 11 SAEs occurred; none of these events were deemed related to study treatment. Grade 3 or 4 laboratory abnormalities (elevated Cr, n=15 [26%], elevated glucose, n=5 [8%], decreased Hgb, n=4 [7%], and elevated potassium, n=3 [5%]) were expected changes in participants undergoing dialysis, and elevated glucose values were seen in participants with diabetes. The area under the plasma concentration-time curve over the dosing interval for the predominant circulating metabolite of SOF (GS-331007) in participants undergoing HD or PD was 1719% (90% CI: 1617–1826%) higher than in participants with eGFR ≥90 mL/min who were enrolled in phase 2/3 studies.

Real-World Studies of SOF/VEL Use in Patients With Renal Impairment

US Claims Database Analysis[4]

Study design and demographics

The risk of ESRD or dialysis among patients with CKD and HCV treated with DAA regimens was evaluated using data sourced from a large US database (IQVIA PharMetrics Plus). The non-concurrent, prospective, observational cohort included claims for adult patients with DAA treatment for HCV infection, CKD diagnosis prior to HCV treatment initiation, and ≥12 months of enrollment prior to HCV treatment start that occurred between January 1, 2006, and March 30, 2019. There was a higher proportion of patients with severe CKD in the non-SOF-based treatment cohort (eg, OBV/PTV/RTV + DSV, OBV/PTV/RTV, EBR/GZR, and GLE/PIB) than in the SOF-based treatment cohort (eg, SOF, LDV/SOF, and SOF/VEL).

Table 1. Baseline Demographics and Disease Characteristics (Telep et al)[4]

Key Demographics and Characteristics	SOF-Based (n=2042)	Non-SOF-Based (n=431)
Age, 18–34/35–44/45–54/ 55–64/65–74/≥75 years, n (%)	27 (1)/59 (3)/295 (14)/ 1300 (64)/331 (16)/30 (1)	14 (3)/11 (3)/64 (15)/ 241 (56)/89 (21)/12 (3)
Male, n (%)	1424 (70)	293 (68)
CKD stage, mild/moderate/severe/unspecified, n (%)	347 (17)/696 (34)/ 123 (6)/876 (43)	65 (15)/161 (37)/ 68 (16)/137 (32)

Effectiveness

The crude incidence rates of ESRD or dialysis were highest for patients with severe CKD and in the cohort that did not receive SOF. After adjustment for age, sex, and significant covariates and PS-weighting by treatment, there was no difference in the risk of ESRD or dialysis between SOF- and non-SOF-based regimens. Similar results were observed when stratified by CKD stage.

Table 2. ESRD/Dialysis Rates in SOF-Based and Non-SOF-Based DAA Cohorts, Stratified by Baseline CKD Stage[a] (Telep et al)[4]

Parameter	Moderate CKD		Severe CKD	
	SOF-Based (n=696)	Non-SOF-Based (n=161)	SOF-Based (n=123)	Non-SOF-Based (n=68)
Events, n	56	8	25	18
Time at risk, PY	1072	138	165	55
Unadjusted rate of ESRD/ dialysis per 100 PY (95% CI)	5.22 (3.95–6.78)	5.78 (2.49–11.39)	15.11 (9.78–22.31)	32.66 (19.35–51.61)
Adjusted and PS-weighted,[b] HR (95% CI)	0.91 (0.41–2.01)	1	0.83 (0.35–2.02)	1

Abbreviations: PY=person-years; HR=hazard ratio.
[a]Results were stratified by participants' baseline CKD stage, where counts of events for each stratum (SOF-based vs non-SOF-based regimens) were ≥5.
[b]HR adjusted for age group, sex, prior diagnosis for acute kidney injury, anemia, hepatic encephalopathy, coronary atherosclerosis, arrhythmia, liver necrosis, essential hypertension, and prior prescriptions for calcium channel blockers or diabetes medication; weighting was based on treatment PS.

Taiwan Prospective Cohort Study of SOF/VEL ± RBV[5]

Study design and demographics

A single-center, prospective cohort study was conducted in Taiwan to evaluate the changes in eGFR in 953 participants with chronic HCV. Participants with detectable HCV RNA (LLOD=15 IU/mL) who received SOF/VEL (400/100 mg) ± RBV for 12 weeks were included in the study. Participants on HD or PD were excluded. The eGFR was assessed at baseline, EOT, and 12 weeks after EOT. SVR12 rates were assessed in both the evaluable population (defined as participants who received ≥1 dose of SOF/VEL ± RBV) and PP population (defined as participants who received ≥1 dose of SOF/VEL ± RBV and had HCV RNA data at SVR12 assessment). Among the total participants, mean eGFR was 85.57 mL/min/1.73 m^2; a total of 130 patients had eGFR ≤60 mL/min/1.73 m^2 and 823 had eGFR >60 mL/min/1.73 m^2 at baseline (Table 3).

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

Key Demographics and Characteristics	SOF/VEL ± RBV		*P*-Value
	Baseline eGFR ≤60 mL/min/1.73 m^2 (n=130)	Baseline eGFR >60 mL/min/1.73 m^2 (n=823)	
Age, mean ±SD, years	74.24±9.99	62.69±14.31	<0.001
Male, n	65	416	0.98
Received RBV, n	12	27	<0.05
HCV RNA, <800,000/≥800,000 IU/mL, n	55/75	268/555	<0.05
Cr, mean ± SD, mg/dL	1.43±0.45	0.83±0.18	<0.001
eGFR, mean ± SD, mL/min/1.73 m^2	47.89±10.25	91.52±22.06	<0.001
Total bilirubin, mean ± SD, mg/dL	0.88±0.56	0.95±0.75	0.23
AST, mean ± SD, U/L	49.88±39.14	52.44±46.99	0.5
ALT, mean ± SD, U/L	48.81±42.07	64.03±69.68	<0.001
Albumin, mean ± SD, g/dL	4±0.54	4.21±0.41	<0.001
FIB-4, ≤3.25/>3.25, n	85/45	641/182	<0.05

Effectiveness

Overall, SVR12 was achieved in 99.2% of participants (870/877) in the PP analysis and in 91.3% (870/953) in the evaluable population analysis; 4 participants experienced virological relapse, and 3 participants did not respond. The SVR12 rates according to baseline eGFR were also reported (Table 4). SVR12 rates did not differ significantly between participants with eGFR ≤60 mL/min/1.73 m^2 and those with eGFR >60 mL/min/1.73 m^2 in subgroups according to age, sex, HBV co-infection, history of hepatocellular carcinoma, prior treatment experience, history of diabetes mellitus, baseline HCV RNA level, and baseline FIB-4 score.

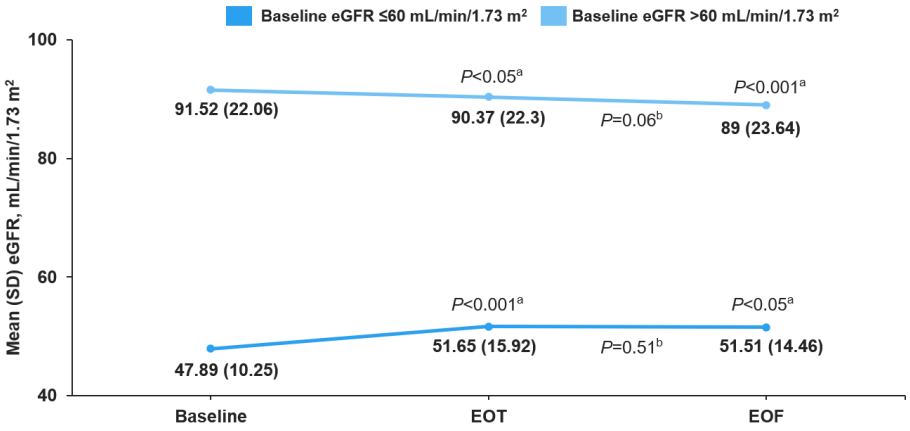
Table 4. SVR12 Rates According to Baseline eGFR (Su et al)[5]

SVR12, n/N (%)	SOF/VEL ± RBV		
	Baseline eGFR <30 mL/min/1.73 m^2 (n=9)	Baseline eGFR 30–60 mL/min/1.73 m^2 (n=121)	Baseline eGFR >60 mL/min/1.73 m^2 (n=823)
Evaluable population	8/9 (88.9)	110/121 (90.9)	752/823 (91.4)
PP	8/8 (100)	110/110 (100)	752/759 (99.1)

Safety

Participants with baseline eGFR ≤60 mL/min/1.73 m^2 showed a significant increase from baseline in eGFR at EOT (P<0.001) to SVR12 assessment (P<0.05). Participants with baseline eGFR >60 mL/min/1.73 m^2 experienced significant decreases from baseline in eGFR at EOT (P<0.05) to SVR12 assessment (P<0.001; Figure 1). In multivariable analyses, participants with higher albumin levels were less likely to experience reductions of >5% in eGFR at EOT (OR, 0.45; 95% CI: 0.28–0.69; P<0.001), whereas participants with a baseline eGFR >60 mL/min/1.73 m² were more likely to experience eGFR reductions at SVR12 assessment than those with a baseline eGFR ≤60 mL/min/1.73 m² (OR, 1.58; 95% CI: 1.03–2.45; P<0.05).

Figure 1. Changes in eGFR (Su et al)[5]



[a]P-value for comparison with baseline eGFR.
[b]P-value for comparison between eGFR at EOT and eGFR at SVR12 assessment.
Note: In the baseline eGFR >60 mL/min/1.73 m^2 cohort, n=823 at baseline, n=652 at EOT, and n=762 at SVR12 assessmentt. In the baseline eGFR ≤60 mL/min/1.73 m^2 cohort, n=130 at baseline, n=107 at EOT, and n=119 at SVR12 assessment.

No SOF/VEL treatment-related deaths occurred during the study. AEs reported in >3% of participants and laboratory AEs are summarized in Table 5.

Table 5. Summary of Safety Results (Su et al)[5]

Events, n (%)		SOF/VEL ± RBV		
		Baseline eGFR ≤60 mL/min/1.73 m^2 (n=130)	Baseline eGFR >60 mL/min/1.73 m^2 (n=823)	Total (N=953)
AEs >3%	Fatigue	9 (6.9)	36 (4.4)	45 (4.7)
	Abdominal discomfort	5 (3.8)	38 (4.6)	43 (4.5)
	Skin itching	5 (3.8)	30 (3.6)	35 (3.7)
Increased total bilirubin	1.5–3 × ULN	6 (4.6)	18 (2.2)	24 (2.5)
	>3 × ULN	0	6 (0.7)	6 (0.6)
Increased AST	3–5 × ULN	2 (1.5)	10 (1.2)	12 (1.3)
	>5 × ULN	1 (0.8)	1 (0.1)	2 (0.2)
Increased ALT	3–5 × ULN	2 (1.5)	4 (0.5)	6 (0.6)
	>5 × ULN	0	3 (0.4)	3 (0.3)

Abbreviation: ULN=upper limit of normal.

Taiwan Retrospective Cohort Study of SOF/VEL ± RBV[6]

Study design and demographics

A multicenter, retrospective study was conducted to assess the effectiveness and tolerance of SOF/VEL ± RBV in patients infected with chronic HCV with decompensated or compensated liver disease and CKD Stage 4 (eGFR <30 mL/min/1.73 m^2) or Stage 5 (eGFR <15 mL/min/1.73 m^2). Data were collected from fifteen academic centers in Taiwan between July 2019 and March 2020. Patients aged ≥20 years with chronic HCV infection (detectable HCV antibody and quantifiable serum HCV RNA for ≥6 months) were included in this analysis. The exclusion criteria included off-label use of SOF/VEL, solid organ transplant (other than failed renal transplant), and virological failures with NS5A-containing DAA regimens.

Table 6. Baseline Demographics and Disease Characteristics (Liu et al)[6]

Key Demographics and Characteristics		SOF/VEL (n=181)	SOF/VEL + RBV (n=10)	Total (N=191)
$eGFR_{CKD-EPI}$, median (range), mL/min/1.73 m^2		8 (2–29)	24 (5–29)	8 (2–29)
CKD stage, Stage 4/Stage 5/HD or PD, n (%)		56 (30.9)/125 (69.1)/ 111 (97.4)/3 (2.6)	7 (70)/3 (30)/ 3 (100)/0	63 (33)/128 (67)/ 114 (97.4)/3 (2.6)
History of renal transplantation, n (%)		8 (4.4)	0	8 (4.2)
Fibrosis stage, n (%)	F0–1/F2/F3/F4[a]	52 (28.7)/92 (50.8)/ 20 (11)/17 (9.4)	0/0/ 0/10 (100)	52 (27.2)/92 (48.2)/ 20 (10.5)/27 (14.1)
	Compensated/decompensated	17 (100)/0	0/10 (100)	17 (63)/10 (37)

Abbreviation: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation.
[a]F4 was defined as a fibrosis index-based score >3.25 and an AST-to-platelet ratio index score >2.

Results

After 12 weeks of treatment, all patients with available data (n=187) had HCV RNA levels <LLOQ. SVR12 rates are shown in Table 7. Among patients with compensated liver disease, 94.6% of patients (53/56) with CKD Stage 4 and 95.2% (119/125) with Stage 5 achieved SVR12. Among patients with decompensated liver disease, 100% of patients (7/7) with CKD Stage 4 and 66.7% (2/3) with Stage 5 achieved SVR12.

Table 7. Effectiveness Outcomes at EOT and at SVR12 Assessment (Liu et al)[6]

HCV RNA <LLOQ (15 IU/mL), n/N (%)		SOF/VEL (n=181)	SOF/VEL + RBV (n=10)	Total (N=191)
At EOT[a]		178/178 (100)	9/9 (100)	187/187 (100)
SVR12	Evaluable population[b]	172/181 (95)	9/10 (90)	181/191 (94.8)
	PP[c]	172/172 (100)	9/9 (100)	181/181 (100)

[a]Data were not available from 4 patients who died or discontinued treatment prematurely.
[b]The evaluable population was defined as patients who received ≥1 dose of SOF/VEL ± RBV.
[c]The PP population was defined as patients with available SVR12 data.

Treatment discontinuation due to general weakness was reported by 1 patient with Stage 4 CKD and Stage F2 fibrosis (Table 8). Changes in eGFR levels in patients not on maintenance dialysis are summarized in Table 9.

Table 8. Summary of Safety Results (Liu et al)[6]

Safety Outcomes, n (%)	SOF/VEL (n=181)	SOF/VEL + RBV (n=10)	Total (N=191)
Any AE	110 (60.8)	9 (90)	119 (62.3)
SAE	18 (9.9)	2 (20)	20 (10.5)
Treatment-related SAE	0	0	0
SOF/VEL discontinuation due to TEAE	1 (0.6)	0	1 (0.5)
Death[a]	6 (3.3)	1 (10)	7 (3.7)

Abbreviation: TEAE=treatment-emergent adverse event.
[a]No deaths were considered related to SOF/VEL or RBV.

Table 9. Changes in eGFR Levels in Patients Not on Maintenance Dialysis (Liu et al)[6]

eGFR	CKD Stage 4 (n=56)	CKD Stage 5 (n=11)
At baseline, mean ± SD, mL/min/1.73 m^2	25.5±3.3	7.3±3.3
At SVR12 assessment, mean ± SD, mL/min/1.73 m^2	27±6.1	7±3.3
P-value for baseline vs at SVR12 assessment	0.06	0.65

Chinese Retrospective Study in Patients With CKD[7]

Study design and demographics

A retrospective study was conducted to assess the effectiveness and safety of SOF/VEL ± RBV in 75 patients with chronic HCV and CKD (eGFR <90 mL/min/1.73 m^2). Data were collected from a single center in China between June 2018 and May 2022. Patients who received SOF/VEL ± RBV (with the RBV dose varying according to weight and renal function) for 12 weeks were included in the study. The primary endpoint was change in renal function during treatment. SVR12 rates and AEs were also evaluated.

Table 10. Baseline Demographics and Disease Characteristics (Yang et al)[7]

Key Demographics and Characteristics		SOF/VEL ± RBV (N=75)
Age, mean (range), years		52 (30–85)
Male, n (%)		58 (77.3)
GT, 1b/2a/3a/3b/6n/unknown, n		1/4/26/37/4/3
CKD stage, 1/2/3a/3b/4/5, n (%)		0/51 (68)/11 (14.6)/1 (1.3)/4 (5.3)/8 (10.7)
Cirrhosis status, n (%)	Compensated	15 (20)
	Decompensated	36 (48)

Results

Overall, SVR12 (HCV RNA <20 IU/mL) was achieved in 98.7% of patients (74/75). The 1 patient who did not achieve SVR12 had decompensated cirrhosis and relapsed liver cancer.

Twenty-two patients (29.3%) reported AEs during treatment with SOF/VEL ± RBV, including hemolysis (n=16), dizziness (n=2), fatigue (n=2), pruritus (n=1), and rash (n=1). All AEs were resolved following supportive treatment, and no SAEs were reported. A worsening in renal function to a higher stage of CKD occurred in 8% of patients (6/75; Table 11).

Table 11. Change in CKD Stages From Baseline to SVR12 Assessment (Yang et al)[7]

Baseline CKD Stage	Off-Treatment CKD Stage, n (%)					
	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5
Stage 2 (n=51)	14 (27.5)	34 (66.7)	2 (3.9)	1 (2)	0	0
Stage 3a (n=11)	1 (9.1)	4 (36.4)	4 (36.4)	2 (18.2)	0	0
Stage 3b (n=1)	0	1 (100)	0	0	0	0
Stage 4 (n=4)	1 (25)	0	0	1 (25)	1 (25)	1 (25)
Stage 5 (n=8)	0	0	0	0	0	8 (100)

Dark purple cells=Improved | White cells=No change | Gray cells=Worsened

Changes in laboratory parameters (eGFR, ALT, and AST) were observed from baseline to SVR12 assessment (**Error! Not a valid bookmark self-reference.**).

Table 12. Changes in Laboratory Parameters From Baseline to SVR12 Assessment (Yang et al)[7]

Laboratory Parameters	SOF/VEL ± RBV (N=75)		
	Baseline	Off-Treatment	*P*-Value
eGFR, mean ± SD, mL/min	63.19±3.01	72.71±4.73	0.078
ALT, mean ± SD, U/L	51.36±35.078	25.3±35.641	<0.05
AST, mean ± SD, U/L	58.1±35.686	42.7±75.758	<0.05

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Abbreviations

AE=adverse event
CKD=chronic kidney disease
DAA=direct-acting antiviral
DCV=daclatasvir
DSV=dasabuvir
EBR=elbasvir
EOT=end of treatment
ESRD=end-stage renal disease
FIB-4=fibrosis-4 index
GLE=glecaprevir
GS-331007=predominant circulating metabolite of sofosbuvir
GT=genotype
GZR=grazoprevir
HD=hemodialysis
LDV=ledipasvir
LLOD=lower limit of detection
LLOQ=lower limit of quantification
OBV=ombitasvir
OR=odds ratio
PD=peritoneal dialysis
PEG-IFN=pegylated interferon
PIB=pibrentasvir
PP=per-protocol
PS=propensity score
PTV=paritaprevir
RBV=ribavirin
RTV=ritonavir
SAE=serious adverse event
SMV=simeprevir
SOF=sofosbuvir
SVR4/12/24=sustained virologic response 4/12/24 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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