GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use Post-Liver Transplantation

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) for the treatment of HCV infection in liver transplant recipients.

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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]

For treatment-naive and TE liver transplant recipients without cirrhosis or with compensated cirrhosis (Child-Pugh A), the recommended regimen is SOF/VEL once daily for 12 weeks.

Clinical Data on SOF/VEL Use in Liver Transplant Recipients

A phase 2, single-arm, open-label study evaluated the safety and efficacy of 12 weeks of SOF/VEL treatment in liver transplant recipients with recurrent, chronic HCV infection (N=79).[2]

- The overall SVR12 rate was 96% (76/79). The most common AEs (≥10% of participants) included headache (24%), fatigue (20%), and cough (10%).[2]

A single-center study evaluated the efficacy and safety of 4 weeks of SOF/VEL treatment following liver transplantation (N=9).[3]

- The SVR12 rate was 78% (7/9). One participant who achieved SVR4 developed multiorgan failure, discontinued SOF/VEL on Day 14, and later achieved SVR12 outside of the study, and 1 participant died on Day 15 secondary to an intra-abdominal hemorrhage. The most common AEs included liver rejection (n=5), constipation (n=4), and GERD (n=3).[3]

Real-World Data on SOF/VEL Use in Liver Transplant Recipients

A single-center, real-world study evaluated the efficacy and safety of initiating 12 weeks of SOF/VEL ± RBV a median of 1 day after liver transplantation in DAA-naive patients and who were HCV RNA+ at the time of surgery (n=43).[4]

- The SVR12 rate was 97.7% (42/43). One patient died secondary to sepsis and subsequent multiorgan failure before completing treatment. No SAEs were reported during SOF/VEL therapy.[4]

Clinical Data on SOF/VEL Use in Liver Transplant Recipients

European Multicenter Study[2]

Study design and demographics

A phase 2, single-arm, open-label study conducted in the UK, Spain, and Switzerland evaluated the safety and efficacy of 12 weeks of SOF/VEL treatment in liver transplant recipients with recurrent, chronic HCV (N=79). The primary efficacy endpoint was SVR12, defined as HCV RNA <15 IU/mL 12 weeks after the end of therapy.

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

Key Demographics and Characteristics		SOF/VEL (N=79)
Age, mean (range), years		62 (45–81)
Male, n (%)		64 (81)
BMI, mean (range), kg/m^2		28 (19–39)
Race, White/Asian/Black, n (%)		65 (82)/12 (15)/2 (3)
HCV GT, 1/2/3/4, n (%)		37 (47)/3 (4)/35 (44)/4 (5)
Cirrhosis, n (%)		14 (18)
TE, n (%)		47 (59)
Last regimen received, n (%)	PEG-IFN ± RBV	26 (55)
	IFN ± RBV	17 (36)
	DAA + RBV ± PEG-IFN	4 (9)
Duration of time from transplant, median (range), years		7.5 (0.3–23.9)
Immunosuppressive therapy, n (%)	Tacrolimus	56 (71)
	Mycophenolic acid	19 (24)
	Cyclosporine	11 (14)
	Azathioprine	9 (11)
	Sirolimus	8 (10)
	Everolimus	5 (6)
	Prednisolone	1 (1)

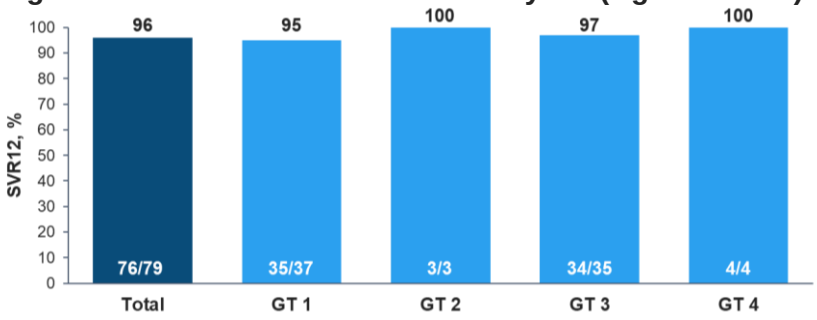
Abbreviations: IFN=interferon; PEG=pegylated.

Efficacy and resistance results[2]

Overall, SVR12 was achieved in 96% of participants (76/79; Figure 1). Two participants experienced virologic failure: 1 participant was treatment naive, had GT 1a without cirrhosis, and relapsed at posttreatment Week 4; and1 participant was TE, had GT 3b without cirrhosis, and relapsed at posttreatment Week 12. Another participant with GT 1b who did not achieve SVR12 discontinued therapy on Day 7 due to an AE of hyperglycemia.

At baseline, NS5A RASs were detected in 31% of participants (24/78) included in the resistance analysis population (participants who achieved SVR12 or had virologic failure). Of these participants, 92% achieved SVR12, including 100% (3/3) of those with GT 3a and the Y93H RAS. NS5B RASs were detected in 6 participants, all of whom achieved SVR12.

Figure 1. SVR12 Rates: Overall and by GT (Agarwal et al)[2]



Safety

SAEs and severe AEs were deemed unrelated to study drug (Table 2). One participant with a history of diabetes discontinued therapy on Day 7 due to an AE of hyperglycemia. No AEs associated with renal dysfunction or clinically meaningful changes in eGFR were reported during study treatment. There were no episodes of acute rejection, and no deaths occurred. No participants required changes to immunosuppression regimens for rejection or drug-drug interactions.

Table 2. Safety Endpoints (Agarwal et al)[2]

Safety Endpoints, n (%)		SOF/VEL (N=79)
Any AE		62 (78)
SAE		3 (4)
Severe AE		3 (4)
Discontinued SOF/VEL due to AE		1 (1)
Most common AEs (≥10% of participants)	Headache	19 (24)
	Fatigue	16 (20)
	Cough	8 (10)
Grade 3 or 4 laboratory abnormalities	Hyperuricemia	4 (5)
	Hyperglycemia	3 (4)
	Lymphocytopenia	1 (1)
	Proteinuria	1 (1)

Single-Center New Zealand Study[3]

Study design and demographics

A single-center study conducted in New Zealand evaluated the efficacy and safety of 4 weeks of SOF/VEL treatment following liver transplantation (N=9). Participants with chronic HCV, no HIV or HBV and no prior HCV NS5A or NS5B inhibitor exposure, and who had an HCV- liver donor were screened for study inclusion. SOF/VEL was initiated on Day 1 following liver transplantation. The primary endpoints were SVR12 and the incidence of AEs that caused study drug discontinuation.

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

Key Demographics and Characteristics	SOF/VEL (N=9)
Age, mean (range), years	61 (56–65)
Male, n (%)	7 (78)
BMI, mean (range), kg/m^2	28 (19–39)
Race, White, n (%)	5 (56)

Key Demographics and Characteristics		SOF/VEL (N=9)
HCV GT, 1/3, n (%)		3 (33)/6 (67)
Pre-transplantation HCV RNA, mean (range), log_{10} IU/mL		6.4 (5.5–7.4)
Pre-transplantation MELD score, 6/7/8/11/13, n (%)		3 (33)/2 (22)/2 (22)/1 (11)/1 (11)
Type of donor, cadaveric/living, n (%)		8 (89)/1 (11)
Immunosuppressive therapy, n (%)	Tacrolimus	9 (100)
	Prednisone	9 (100)
	Methylprednisolone	5 (56)
	Mycophenolate mofetil	1 (11)

Efficacy and safety

The SVR12 rate was 78% (7/9). One participant who achieved SVR4 developed multiorgan failure, discontinued SOF/VEL on Day 14, and later achieved SVR12 outside of the study, and 1 participant died on Day 15 secondary to an intra-abdominal hemorrhage.

The following AEs occurred in >1 participant: liver transplant rejection (n=3; each occurred during the study and resolved on study drug) and postprocedural bile leak (n=2). None of the Grade 3 AEs or SAEs were deemed treatment related.

Table 4. Safety Endpoints (Gane et al)[3]

Safety Endpoints, n or n (%)		SOF/VEL (N=9)
Any AE		9 (100)
Most common AEs	Liver rejection	5
	Constipation	4
	GERD	3
Grade 3 AE		5 (56)
SAE		5 (56)
Discontinued due to AE		1 (1)
Death		1 (11)

Real-World Data on SOF/VEL Use in Liver Transplant Recipients

Single-Center Italian Study[4]

Study design and demographics

A single-center, real-world, retrospective study conducted in Italy between January 2019 and July 2022 evaluated the efficacy and safety of initiating DAA therapy immediately after liver transplantation in patients with HCV-related cirrhosis and who were HCV RNA+ at the time of transplantation. Of the 49 patients included in the study, 43 were DAA naive and initiated 12 weeks of SOF/VEL ± RBV, and 6 were NS5A inhibitor experienced and received 12 weeks of SOF/VEL/VOX.

Table 5. Baseline Demographics and Disease Characteristics of DAA-Naive Patients Treated With SOF/VEL + RBV (Saracco et al)[4]

Key Demographics and Characteristics	SOF/VEL ± RBV (n=43)
Age, median (IQR), years	55 (52–58)
Male, n (%)	35 (81.4)

Key Demographics and Characteristics		SOF/VEL ± RBV (n=43)
BMI, median (IQR), kg/m^2		22.9 (20.9–24.7)
HCC, n (%)		33 (76.7)
HCV GT, 1/3, n (%)		23 (53.3)/15 (35)
At liver transplantation	MELD score, median (IQR)	10 (8–17)
	HCV RNA, median (IQR), $\log_{10}$ IU/mL	5.6 (4.9–6.1)
Donor characteristics	HCV antibody+, n (%)	6 (14)
	HCV RNA status, positive/negative, n	5/1
	Hepatitis B core antibody+, n (%)	6 (14)

Efficacy and safety

The median time from liver transplantation to SOF/VEL ± RBV initiation was 1 day (Day 0, n=7; Day 1, n=32; Day 2, n=2; Day 18, n=1; and Day 30, n=1). Both patients who completed treatment achieved HCV RNA <15 IU/mL within 8 weeks of treatment. Of the patients in the SOF/VEL group, 42/43 (97.7%) achieved SVR12, and 41 (95.3%) were alive and were HCV RNA- after a median (IQR) duration of follow-up of 690 (439–1013) days.

One patient died due to sepsis and subsequent multiorgan failure on postoperative Day 27 (26 days after treatment with SOF/VEL was initiated), with an HCV RNA<15 IU/mL. Another patient died on postoperative Day 386 due to a recurrence of HCC. No SAEs were reported over the course of SOF/VEL treatment. No unusual adjustments to immunosuppression regimens were required.

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Agarwal K, Castells L, Mullhaupt B, et al. Sofosbuvir/velpatasvir for 12 weeks in genotype 1-4 HCV-infected liver transplant recipients. *J Hepatol.* 2018;69(3):603-607. https://www.ncbi.nlm.nih.gov/pubmed/29886154
3. Gane EJ, Fuentes AB, Hyland RH, et al. Short-Duration Sofosbuvir/Velpatasvir Safe and Effective in Treating HCV Infection Immediately After Liver Transplant [Poster 604]. Paper presented at: AASLD: The Liver Meeting® 2018; 09-13 November, 2018; San Francisco, CA.
4. Saracco M, Tandoi F, Maletta F, Balagna R, Romagnoli R, Martini S. Early post-liver transplant use of direct-acting antivirals in naive and NS5A inhibitor-experienced HCV patients. *J Viral Hepat.* 2023;30:201-208.

Abbreviations

AE=adverse event
DAA=direct-acting antiviral
GERD=gastroesophageal reflux disease
GT=genotype
HCC=hepatocellular carcinoma
MELD=model for end stage liver disease
NS5A/NS5B=nonstructural protein 5A/5B
RAS=resistance-associated substitution
RBV=ribavirin
SAE=serious adverse event
SOF=sofosbuvir
SVR4/12=sustained virologic response 4/12 weeks after end of treatment
TE=treatment-experienced
VEL=velpatasvir
VOX=voxilaprevir

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
https://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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