GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Crushing or Splitting Tablets

This document is in response to your request for data regarding the crushing or splitting of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) tablets.

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]

There is no information in the SOF/VEL product labeling about the crushing or splitting of SOF/VEL tablets. Oral pellets should not be chewed to avoid a bitter aftertaste.

SOF has a solubility of ≥2 mg/mL across the pH range of 2 to 7.7 at 37°C and is slightly soluble in water. VEL is practically insoluble (<0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (>36 mg/mL) at pH 1.2.

Clinical Data on Crushing or Splitting SOF/VEL Tablets

- There are no Gilead studies evaluating the efficacy, safety, and PK parameters of a disintegrated, crushed, or split SOF/VEL tablet versus the whole tablet in a randomized controlled trial.
- In the DONATE HCV Trial (N=35), for participants who could not swallow medications, SOF/VEL tablets were crushed, mixed with saline, and administered via an orogastric, NG, or PEG tube. The SVR12 rate was 100% (35/35). No treatment related AEs were reported.[2,3]

Case Series/Reports on Crushing or Splitting SOF/VEL Tablets

- In a case series that included 19 patients who received crushed SOF/VEL, 95% of patients achieved SVR12 and there were no provider-reported on-treatment AEs or treatment discontinuations.[4]
- In a case series that included 5 patients who received crushed or split SOF/VEL ± RBV, all patients with follow-up data (n=4) achieved SVR12 and no patients reported severe AEs.[5]
- Five case reports described outcomes in patients who received crushed SOF/VEL. Of the 4 patients who completed treatment, all achieved SVR12. Three patients had no treatment-related AEs, and 1 patient reported headache and fatigue.[6-9] One patient achieved viral clearance at Week 4 but died before SVR12 could be evaluated.[10]

Clinical Data on Crushing or Splitting Tablets

SOF/VEL tablets are not enteric-coated and do not possess a sustained-release mechanism. According to the European Summary of Product Characteristics, it is recommended that the film-coated tablet is not chewed or crushed due to bitter taste.[11]

DONATE HCV Trial

Study design and demographics

A single-center, open-label pilot study was conducted to evaluate the safety of HCV-mismatched transplants in HCV-negative participants on the waitlist for heart or lung transplantation from HCV-positive donors between March 1, 2017, and July 31, 2018.[2]

There were 44 participants (36 lung transplants and 8 heart transplants) who received an organ from a donor with active HCV infection (NAT+), regardless of HCV GT; starting on the day of transplantation, participants received SOF/VEL for 4 weeks. The median (range) ages of the lung transplant HCV NAT+ donors and recipients were 32 (21–53) and 61 (41–71) years, respectively. Males comprised 39% (11/28) of lung transplant recipients, who were on a waitlist for a median (range) of 136 (17–2616) days. Twenty-six lung transplant recipients (93%) were White, and the median lung allocation score was 33.31. The median (range) ages of the heart transplant HCV NAT+ donors and recipients were 27 (24–42) and 51 (23–68) years, respectively. Among the heart transplant recipients, 86% (6/7) were male, 86% (6/7) were White, and the median (range) duration of time on a waitlist was 559 (90–2366) days. Illicit drugs were used ≤6 months of death in 71% of the lung and heart donors.[2]

For participants who could not swallow medications, SOF/VEL tablets were crushed, mixed with saline, and administered via an orogastric, NG, or PEG tube. This was most often required in the immediate post-transplant period for at least the first 2 doses of SOF/VEL prior to extubation. No issues were encountered with enteral therapy in this study. Primary outcomes were SVR12 and graft survival 6 months after transplantation. Outcomes are reported in 35 participants who had ≥6 months of follow-up.[3]

Table 1. Overall Baseline Characteristics of HCV-Mismatched Transplants (Woolley et al)[2]

Key Characteristics	HCV-Mismatched Organ Transplants (N=44)
Follow-up duration, median (IQR), days	284 (171–385)
Donor HCV VL, median (IQR), IU/mL	890,000 (276,000–4.63 million)
HCV GT, 1/2/3/indeterminate, %	61/17/17/5

Efficacy[2]

SVR12 and SVR24 were achieved by all participants (100%; 35/35). Nearly all (95%; 42/44) transplant recipients had a detectable HCV VL after transplant, and the median (IQR) initial VL was 1800 (800–6180) IU/mL. By post-transplant/treatment Week 2, all recipients had an undetectable VL. Twenty-seven of the 35 participants (77%) had positive HCV-Ab tests at post-transplant Week 1, and half (49%; 17/35) had positive HCV-Ab tests at post-transplant Month 6. Nearly all participants (94%; 15/16) with ≥12 months of follow-up had graft survival, and 1 recipient of a heart transplant died at post-transplant Month 8 (disseminated bacterial infection, deemed unrelated to treatment by study investigators).

Safety

No AEs or serious AEs were deemed to be related to the study medication by study investigators. Ab-mediated rejection was observed in 1 participant (4%) who received a lung transplant from an HCV-positive donor and in 5 participants (15%) who received lung transplants from HCV-negative donors.[2] Nearly all (34/35) of the HCV-mismatched transplant recipients had Grade 3 or 4 AEs, which resulted in 155 AEs. The following Grade 3 or 4 AEs (frequency ≥5) occurred ≤30 days of transplantation: anemia, atrial fibrillation, hypotension, right ventricular dysfunction, and respiratory failure. The following Grade 3 or 4 AEs (frequency ≥5) occurred >30 days after transplantation: rejection, renal insufficiency, pneumonia, and pleural effusion.[2,3]

Case Series/Reports Crushing or Splitting Tablets

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on uncontrolled observational data. In addition, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of case reports include the retrospective design and publication bias.[1,2]

Case Series in Patients Who Received Crushed SOF/VEL[4]

A multicenter case series evaluated the safety (AEs and treatment discontinuation) and efficacy (SVR12) of crushed SOF/VEL for the treatment of HCV in 19 patients (aged 26–69 years) from thirteen US-based medical centers. Overall, 11 patients were female, 11 and 8 patients had HCV GT 1/3, HCV VL ranged from 3.71 to 7.66 log IU/mL, and the administration route was the following: oral (n=8), PEG tube (n=7), NG tube (n=3), and jejunostomy tube (n=1). The carrier for SOF/VEL was water (n=5), soda (n=2), juice (n=2), other (n=8), or none (n=3). Eighteen patients received crushed SOF/VEL for a treatment duration of 84 days and 1 patient received crushed SOF/VEL for 73 days. Treatment dose interruptions were reported in 3 patients (causes for dose interruption were not reported). Ninety-five percent of patients (18/19) achieved SVR12. There were no provider-reported on-treatment AEs or treatment discontinuations.

Case Series with SOF/VEL ± RBV After Tablet Manipulation[5]

A multicenter, retrospective case series evaluated the safety (AEs) and efficacy (SVR12) associated with direct-acting antiviral tablet manipulation in 9 patients (SOF/VEL ± RBV, n=5). Tablets were manipulated due to difficulty swallowing (history of head or neck cancer, n=6; unable to swallow large tablets, n=1), short gut syndrome that required enteral feeding (n=1), or inpatient intubation (n=1).

Table 2. Summary of Cases That Required SOF/VEL Tablet Manipulation[5]

Sex	Race	GT	Fibrosis Stage	TN or TE	Drug Regimen	Method of Administration
Male	White	3	F2–F3	TN	SOF/VEL	Crushed, PEG tube[a]
Male	Black	3	F2	TN	SOF/VEL	Crushed, by mouth[b]
Female	White	3	F0	TN	SOF/VEL	Split in half, taken on gelatin[b]
Female	White	1a	F0	TE[c]	SOF/VEL	Crushed, sprinkled on applesauce[a]

Sex	Race	GT	Fibrosis Stage	TN or TE	Drug Regimen	Method of Administration
Female	White	3	F4	TE[d]	SOF/VEL + RBV	Split in quarters, taken by mouth[a]

Abbreviation: TE=treatment experienced.
[a]Patient reported ≥1 missed dose.
[b]Patient reported no missed doses.
[c]Patient received prior treatment with simeprevir and SOF.
[d]Patient received prior HCV treatment with interferon.

HCV RNA was undetectable for all patients while on treatment and at the end of treatment. All patients on SOF/VEL with follow up data (n=4) achieved SVR12; one patient was lost to follow up. Unpleasant taste was reported by some patients in the study; however, no patients reported severe AEs.

Table 3. Summary of Case Reports of Patients Receiving Crushed SOF/VEL[6-10]

	Presentation	Case Details	Resolution	Notes
Lalanne et al, 2019	70-year-old female, TN with a history of oropharyngectomy	Patient was diagnosed with HCV GT 1b infection with high VL of 6.8 log IU/mL and was prescribed 12 weeks of SOF/VEL treatment. Due to her oropharyngectomy, she was unable to swallow tablets; thus, SOF/VEL was crushed and administered with a meal and an acidic beverage. Therapeutic drug monitoring was performed on Day 1 and Weeks 1 and 10 after initiation of therapy.	The patient's HCV VL rapidly decreased and was undetectable after 4 weeks of treatment; after the patient completed 12 weeks of treatment, the HCV VL continued to be undetectable.	Compared with the usual C_{max} for the individual drugs, there was an increase in the concentrations of SOF and VEL when crushed, which indicated increased absorption.
Mogul et al, 2020	62-year-old female, TN, non-cirrhotic, chronic HCV GT 4 with a history of dysphagia	Patient had an HCV RNA VL of 108,540 IU/mL and was prescribed 12 weeks of SOF/VEL treatment. Due to her dysphagia, she was unable to swallow tablets whole. She was instructed to crush the tablet and ingest it after mixing it with a soft food, such as applesauce.	At Weeks 4 and 12, the patient's HCV VL was undetectable. SVR12 was achieved. At Week 4, her AST/ALT concentrations returned to within normal range.	During SOF/VEL treatment, the patient experienced headache and fatigue; resolution of these events occurred early during the course of treatment.
Van Seyen et al, 2020	54-year-old male with chronic HCV GT 2 and history of stroke resulting in weakness PEG tube placement	Patient was prescribed 12 weeks of SOF/VEL, which was crushed, dissolved in water, and administered via PEG tube. PK curves were recorded at steady state on Day 15. On Day 16, the patient ingested a whole tablet of SOF/VEL while being supervised medically, and a second PK curve was recorded. SOF exposure after administration of a crushed tablet was similar to exposure after administration of a whole tablet (2577 µg·h/L and 2502 µg·h/L, respectively). However, administration of crushed SOF/VEL resulted in a 35% decrease in VEL C_{max} compared with the C_{max} observed after administration of a whole tablet; this decrease was not considered clinically relevant.	The patient's VL was reduced to 49.6 IU/mL after 2 weeks of treatment. The patient completed 12 weeks of SOF/VEL treatment and achieved SVR12. No AEs were reported.	The concentrations of SOF and VEL after administration of the crushed tablet were similar to or higher than population-based reference values after administration of a whole SOF/VEL tablet.
Murayama et al, 2021	36-year-old female, TN, with chronic HCV, decompensated cirrhosis, with a history of intractable epilepsy, cerebral palsy, and thrombocytopenia	Patient was prescribed 12 weeks of SOF/VEL, but she was unable to swallow tablets due to dysphagia. Crushed SOF/VEL was administered via NG tube.	After 2 weeks of SOF/VEL treatment, HCV-RNA levels were undetectable, and no AEs were reported throughout the 12 weeks of therapy. The patient achieved SVR at both 12 and 24 weeks post treatment.	The patient was on multiple medications including clarithromycin (pneumonia), valproic acid + clobazam + zonisamide (intractable epilepsy), furosemide + tolvaptan (ascites, leg edema).
Pluckrose et al, 2022	31-year-old female with a history of alcoholic cirrhosis was HCV-negative and received a liver transplantation from an HCV NAT+ donor	Patient required a diverting loop ileostomy at the time of liver transplantation. Postoperative complications included pancreatitis, mucormycosis infection that required an above-the-knee amputation, and HCV. On postoperative Day 39, a 12-week course of SOF/VEL was initiated; SOF/VEL was crushed, mixed with water, and administered via NG tube.	Viral clearance was achieved at Week 4 of treatment, but the patient died due to sepsis on postoperative Day 77.	The patient completed 39/84 treatment days before she died.

References

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Abbreviations

Ab=antibody
AE=adverse event
C_{max}=maximum concentration
GT=genotype
NAT=nucleic acid test
NG=nasogastric
PEG=percutaneous endoscopic gastrostomy
PK=pharmacokinetic
RBV=ribavirin
SOF=sofosbuvir
SVR12=sustained virologic response 12 weeks after end of treatment
SVR24=sustained virologic response 24 weeks after end of treatment
TN=treatment naïve
VEL=velpatasvir
VL=viral load

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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