Use of HCV Antivirals in Patients with Swallowing Difficulties: Focus on Epclusa and Mavyret

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Overview

- **HCV Overview**: Chronic hepatitis C (HCV) impacts around 70 million people worldwide and can lead to severe liver complications, including cirrhosis and hepatocellular carcinoma.
- According to data from the 2017-2020 NHANES survey, an estimated 2.2 million individuals in the United States were HCV RNA positive during this period. Over half of those living with HCV are aged 55 or older, with the highest prevalence (2.4%) observed among individuals aged 55-64.
- In 2021, the CDC identified 107,540 new chronic HCV diagnoses across the U.S. The age group with the newest cases was 30-39, followed by individuals aged 60 and older.
- **Antivirals of Focus**: Epclusa (sofosbuvir/velpatasvir) and Mavyret (glecaprevir/pibrentasvir) have shown over 95% cure rates in HCV across multiple genotypes

Significance

Prevalence of Swallowing Difficulties: Approximately 15% -20% of older adults report dysphagia; with an increased risk in adults with debilitating conditions.

Impact on Adherence

Maximizing Clinical Outcomes

Epclusa

Composition: Epclusa contains sofosbuvir a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and targets multiple HCV genotypes.

Indications: the treatment of adult patients and pediatric patients 3 years of age and older with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infections:

- Without cirrhosis or with compensated cirrhosis
- HCV/HIV-1 coinfection
- With decompensated cirrhosis for use in combination with ribavirin

Dosing: 12-week regimen

- Tablets: One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily with or without food.
- Oral pellets: once daily with or without food. In pediatric patients less than 6 years of age, administer the oral pellets with food to increase tolerability.
  - Pediatric patients are dosed by weight.

Administration: 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.

Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.

Gilead Sciences, Inc. is providing this document to you, a US Healthcare Professional, in response to your unsolicited request for medical information.

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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.

"*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.*"

Mavyret

Composition: Mavyret combines glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor effective against HCV genotypes 1-6.

Indications: the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infections:

- Without cirrhosis or with compensated cirrhosis
- HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

Dosing: 8-week regimen except in specific patient populations.

- Tablets: Three tablets (glecaprevir 300 mg and pibrentasvir 120 mg) taken orally once daily with food.
- Oral pellets: Recommended dose by the product labeling with soft food.
  - Pediatric patients aged 3-12 are dosed by weight.

Administration: There is no information in the product labeling about the crushing or splitting of tablets. Oral pellets should not be chewed or crushed.

CLINICAL TRIALS

DONATE HCV TRIAL

This clinical trial, explored the viability of heart and lung transplants from HCV-positive donors into HCV-negative recipients, using Epclusa as a preemptive antiviral therapy.

Population: The study included 44 transplant recipients (36 lung and 8 heart transplants) from HCV-infected donors. Some recipients experienced swallowing difficulties due to intubation or other complications associated with transplant recovery.

Treatment Protocol: Epclusa (400 mg sofosbuvir and 100 mg velpatasvir) was given once daily for 4 weeks. Administration began within hours post-transplant to block viral replication, simulating post-exposure prophylaxis rather than treatment for established HCV infection.

- For these patients, the tablets were crushed, mixed with saline, and administered via alternative routes, including orogastric, nasogastric (NG), and percutaneous endoscopic gastrostomy (PEG) tubes.
- **Despite this modified administration, all 35 patients achieved sustained virologic response (SVR12),** indicating undetectable HCV RNA levels 12 weeks after completing the antiviral therapy. No treatment-related adverse events were reported, highlighting both the efficacy and safety of crushed Epclusa under these conditions

Woolley AE, Singh SK, Goldberg HJ, et al. Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. N Engl J Med. 2019;380(17):1606-1617.
https://www.ncbi.nlm.nih.gov/pubmed/30946553

CASE SERIES

CASE SERIES 1

- **Study Methods**
  - Data were gathered from 13 U.S. medical centers, with providers submitting deidentified records for patients treated with crushed Epclusa. Information collected included patient demographics, HCV genotype, fibrosis score, adverse events, and SVR (sustained virologic response) rates, which indicate viral clearance 12 weeks post-treatment.
- **Results**
  - **Participants**: 19 patients (11 female, 8 male); predominantly White (11), followed by Hispanic (4), Black (3), and other (1).
  - **HCV Genotypes**: Most common genotypes were 1 (11 patients) and 3 (8 patients).
  - **Fibrosis Scores**: Available for 15 patients, ranging from F0 (minimal fibrosis) to F4 (severe fibrosis).
  - **Administration: Patients received crushed Epclusa orally, via NG tube, PEG tube, or J-tube, with solvents such as soda, juice, and water.**
- **Efficacy**: 100% of patients with end-of-treatment data had an undetectable viral load, and 95% achieved SVR12.
- **Safety**: No patients reported on-treatment adverse events, and no therapy discontinuations occurred. Three patients had dose interruptions but completed the full course of therapy.

Joshi S, Cohen M, Katz R, et al. A Case Series of Safety and Efficacy of Crushed Sofosbuvir/Velpatasvir in Hepatitis C Infected Patients [Poster]. Paper presented at: American Association for the Study of Liver Diseases (AASLD): The Liver Meeting Digital Experience; 12-15 November 2021.

CASE SERIES 2: Tablet Manipulation of DAAs for HCV Treatment

The study reviewed cases of patients prescribed DAA therapies, including Epclusa, who required tablet manipulation from 2013 to 2019. Data was collected on demographics, HCV genotype, treatment methods, and outcomes. Reasons for manipulation included dysphagia due to cancer or anatomical changes, short gut syndrome, and post-transplant intubation. Patients received 12 weeks of treatment, and adherence was monitored.

- **Results**
  - **Participants**: 10 patients were included, with a median age of 61 years; 60% were male, 50% were Black, and the other half were White.
  - **HCV Genotypes and Treatments**: The most common genotype was 1a. Patients received sofosbuvir/velpatasvir (50%), ledipasvir/sofosbuvir (30%), or glecaprevir/pibrentasvir (20%). 70% of the patients had tablets crushed, while the remainder had tablets split.

- **Outcomes**:
  - **Efficacy**: All patients achieved undetectable viral loads within 56 days of treatment initiation, with a median time to viral suppression of 33 days. Those with follow-up data achieved SVR12.
  - **Adverse Events**: No severe adverse events were reported, though four patients noted an unpleasant taste. Adherence was generally high, with most patients completing treatment with four or fewer missed doses.

Whelchel K, Zuckerman AD, Koren DE, Derrick C, Bouchard J, Chastain CA. Crushing and Splitting Direct-Acting Antivirals for Hepatitis C Virus Treatment: A Case Series and Literature Review. Open forum infectious diseases. 2021;8(11):ofab525.

CASE REPORTS

Summary of Case Reports of Patients Receiving Crushed SOF/VEL

	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.

Lalanne S, Jezequel C, Tron C, et al. TDM-Guided Crushed Sofosbuvir-Velpatasvir Treatment: A Case Study [Accepted]. Ther Drug Monit. 2019. https://www.ncbi.nlm.nih.gov/pubmed/31809407
Mogul A, Teixeira E, McAuliffe L, Promrat K, Zullo AR. Effectiveness of Crushed Sofosbuvir-Velpatasvir in a Patient with Dysphagia. Am J Health Syst Pharm. 2020. https://www.ncbi.nlm.nih.gov/pubmed/31930300

Summary of Case Reports of Patients Receiving Crushed SOF/VEL

	Presentation	Case Details	Resolution	Notes
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.

Van Seyen M, Samson AD, Cullen L, et al. Crushed Application of Sofosbuvir and Velpatasvir in a Patient with Swallowing Disorder [Journal Pre-Proof]. Int J Antimicrob Agents. 2020. https://www.ncbi.nlm.nih.gov/pubmed/32156618

Murayama A, Tajiri K, Kanegane C, Murakami J, Hayashi Y, Yasuda I. Successful Treatment with Crushed Sofosbuvir/Velpatasvir of a Patient with Decompensated Cirrhosis C and Thrombocytopenia. Case Rep Gastroenterol. 2021;15(2):729-735.

*Pluckrose DM, Szczepanik A, Bova SE, Freedman SR. Hepatitis C viral clearance with coadministration of crushed sofosbuvir/velpatasvir and high-dose pantoprazole after liver transplantation [Accepted Manuscript]. Am J Health Syst Pharm. 2022.*https://www.ncbi.nlm.nih.gov/pubmed/35675479

National Liver Entities' Guidelines

- **The AASLD/EASL guidelines do not provide specific recommendations on the use of HCV antivirals in patients with swallowing difficulties.**

Summary

References

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