GILEAD | Medical Information

Harvoni® (ledipasvir/sofosbuvir) Crushing or Splitting of Tablets

This document is in response to your request for information regarding Harvoni® (ledipasvir/sofosbuvir [LDV/SOF]) and the crushing or splitting of 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/harvoni/harvoni_pi.

Product Labeling[1]

There is no information in the LDV/SOF US product labeling about the crushing or splitting of film-coated LDV/SOF tablets; therefore, it is not recommended that LDV/SOF be administered as a crushed or split tablet.

For the individual components of LDV/SOF, LDV is practically insoluble (<0.1 mg/mL) across the pH range of 3 to 7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL), and 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.

Please refer to the US product labeling for complete product information on LDV/SOF oral pellets.

Available Data on Crushing or Splitting LDV/SOF

There are no Gilead randomized controlled trials that have compared the pharmacokinetic parameters of a disintegrated, crushed, or split LDV/SOF tablet to the whole tablet.

LDV/SOF tablets are not enteric-coated, do not possess a sustained-release mechanism, and are not scored. According to the European Summary of Product Characteristics, it is recommended that film-coated tablets are not chewed or crushed due to their bitter taste.[2]

Case Series/Reports on Crushing or Splitting LDV/SOF

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. Additionally, 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.[3]

Summarized below are a case series and four clinical case reports of patients who received crushed or split LDV/SOF tablets. All patients with follow-up data achieved SVR12.[4-8]

Case series[4]

A multicenter, retrospective case series evaluated the safety and efficacy associated with direct-acting antiviral tablet manipulation in 9 patients, including 3 patients who were treated with LDV/SOF (Table 1). 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 1. Summary of Cases That Required LDV/SOF Tablet Manipulation[4]

Sex	Race	GT	Fibrosis Stage	TN or TE	Method of Administration
Male	Black	1a	F2–F3	TN	Halved, by mouth[a]
Male	Black	1a	F0	TE[b]	Crushed, by mouth with orange juice[a]
Male	Black	1a	F0–F1	TN	Crushed, by mouth[c]

[a]Patient reported no missed doses.
[b]Patient received prior HCV treatment with interferon.
[c]Patient reported ≥1 missed dose.

HCV RNA was undetectable for all patients while on treatment and at the end of treatment. Only 1 of the 3 patients on LDV/SOF had follow up data, and SVR12 was achieved.

Unpleasant taste was reported by some patients; no patients reported severe AEs.

Case Reports

Crushed LDV/SOF tablets administered via gastrostomy button[5]

A 19-year-old, TN, female with HCV GT 1, no cirrhosis, and HIV co-infection received crushed LDV/SOF mixed with water that was administered through a gastrostomy button once daily for 12 weeks. Liquid HIV antiretroviral agents and an H2 blocker, among several other medications, were also administered via a gastrostomy button. Although concentrations of LDV and SOF were not measured, SVR12 was achieved. Safety information was not provided.

Crushed LDV/SOF tablets administered via PEG tube in patient with HIV co-infection[8]

A 57-year-old, TN, female with HCV GT 1b, no cirrhosis, and HIV co-infection received crushed LDV/SOF tablet dissolved in water that was administered through a PEG tube once daily for 12 weeks. The patient was also treated for sarcoma of the throat with IV olaratumab and an IV H2 blocker as pre-medication every 3 weeks. Furthermore, HIV antiretroviral agents among several other medications, were administered via the PEG tube. She achieved SVR12 with HCV RNA load less than the lower limit of quantification (<12 IU/mL) at the end of treatment. The patient reported fatigue; however, symptoms did not differ from those experienced prior to starting treatment; no treatment-related severe AEs were reported.

Ground LDV/SOF tablets[6]

A 47-year-old TN male with HCV GT 1b and concomitant short bowel syndrome following a complicated course of Crohn's disease received mechanically ground LDV/SOF for 12 weeks. He achieved SVR12, and HCV RNA levels were undetectable from post-treatment Week 4 through Week 24. No AEs were reported.

Crushed LDV/SOF tablets administered via PEG tube in patient with cirrhosis[7]

A 61-year-old TE male with HCV GT 1, cirrhosis, and concomitant use of a H2 blocker (proton pump inhibitor was discontinued prior to LDV/SOF therapy) received crushed LDV/SOF tablets dissolved in water that were administered through a PEG tube due to a history of pharyngeal ulceration. He achieved SVR12 after 24 weeks of crushed LDV/SOF tablets given through the PEG tube. No AEs were reported.

References

1. Enclosed. Gilead Sciences Inc, HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
2. Harvoni. Gilead Sciences Inc. Harvoni 90mg/400mg or 45mg/200mg film-coated tablets and 33.75mg/150mg or 45mg/200mg coated granules. Summary of Product Characteristics. County Cork, Ireland UC.
3. Nissen T, Wynn R. The Clinical Case Report: A Review of Its Merits and Limitations. *BMC Res Notes.* 2014;7:264. https://www.ncbi.nlm.nih.gov/pubmed/24758689
4. 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 Infect Dis.* 2021;8(11):ofab525.
5. Fulco PP, Sterling RK, Lavoie SR. Administration of Crushed Ledipasvir-Sofosbuvir Tablets Via Gastrostomy Button in a Patient Coinfected with HIV and Hepatitis C Virus. *Am J Health Syst Pharm.* 2017;74(21):1761-1762. https://www.ncbi.nlm.nih.gov/pubmed/29070496
6. von Felden J, Scheurich C, Yamamura J, et al. Successful Treatment of Chronic Hepatitis C with Ground Ledipasvir/Sofosbuvir in a Patient with Crohn's Disease and Short Bowel Syndrome. *J Viral Hepat.* 2018;25:214-215. https://www.ncbi.nlm.nih.gov/pubmed/28783205
7. Jindracek L, Stark J. Treatment of Chronic Hepatitis C Virus Infection With Crushed Ledipasvir/Sofosbuvir Administered via a Percutaneous Endoscopic Gastrostomy Tube. *J Pharm Pract.* 2018.
8. Huffman V, Andrade DC, Sherman E, Niu J, Eckardt PA. Treatment of chronic hepatitis C virus infection with crushed ledipasvir/sofosbuvir administered through a percutaneous endoscopic gastrostomy tube in a patient with HIV coinfection. *Am J Health Syst Pharm.* 2021;78(1):36-40.

Abbreviations

AE=adverse event
GT=genotype
H2=histamine type 2 receptor
LDV=ledipasvir
PEG=percutaneous endoscopic gastrostomy
SOF=sofosbuvir
SVR12=sustained virologic response 12 weeks after end of treatment
TE=treatment-experienced
TN=treatment-naive

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Harvoni US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_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 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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