GILEAD | Medical Information

# Epclusa® (SOF/VEL), Harvoni® (LDV/SOF), Sovaldi® (SOF), Vosevi® (SOF/VEL/VOX) Drug Interaction With Amiodarone

This document is in response to your request for information regarding Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]), Harvoni® (ledipasvir/sofosbuvir [LDV/SOF]), Sovaldi® (sofosbuvir [SOF]), and Vosevi® (sofosbuvir/velpatasvir/voxilaprevir [SOF/VEL/VOX]) and the drug interaction with amiodarone.

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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;**
**www.gilead.com/-/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_pi;**
**www.gilead.com/-/media/files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi;**
**www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.**

## Product Labeling[1-4]

### Serious Symptomatic Bradycardia When Coadministered With Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with a SOF-containing regimen. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a SOF-containing regimen (LDV/SOF). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with SOF/VEL, LDV/SOF, SOF, or SOF/VEL/VOX is not recommended. For patients taking amiodarone who have no other alternative viable treatment options and who will be coadministered SOF/VEL, LDV/SOF, SOF, or SOF/VEL/VOX:

- Counsel patients about the risk of symptomatic bradycardia.
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking a SOF-containing regimen who need to start amiodarone therapy due to no other alternative viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting a SOF-containing regimen should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems.

## Detailed Information on Postmarketing Cases[5]

Nine cases of symptomatic bradycardia have been reported during postmarketing in patients receiving amiodarone with either LDV/SOF or SOF in combination with another DAA (DCV or SMV). Seven patients were also receiving a beta blocker. Six cases occurred within the first 24 hours of coadministration, and the remaining 3 cases occurred within the first 2 to 12 days following HCV treatment initiation. One case resulted in a fatal cardiac arrest, and 3 cases required pacemaker intervention. In 3 cases, rechallenging with HCV treatment in the setting of continued amiodarone therapy resulted in recurrence of symptomatic bradycardia. In 1 case, discontinuation of amiodarone followed by rechallenging with HCV treatment after 8 weeks did not result in recurrent bradycardia. Three of the 9 cases occurred in patients receiving LDV/SOF, 5 cases were in patients receiving SOF + DCV, and 1 case was in a patient receiving SOF + SMV. Because the number of patients taking amiodarone who have been exposed to SOF is unknown, it is not possible to estimate the incidence of these events.

## Clinical Data on the Concurrent Use of Amiodarone With SOF-Based Regimens

### French Cohort Study[6-8]

A prospective, single-center analysis evaluated the incidence of arrhythmia and conduction disorder in 415 participants treated with SOF-based regimens. Arrhythmia was reported during the treatment of 4 participants with cirrhosis and 1 participant with F3 fibrosis. They were taking SOF + DCV (n=3), SOF + SMV and retreatment with SOF + RBV (n=1), or SOF + DCV + RBV (n=1). Rhythm abnormalities included sinus node dysfunction (n=1), junctional tachycardia (n=1), syncopal sinus bradycardia (n=1), intermittent third-degree atrioventricular block with syncope (n=1), and paroxysmal atrial flutter (n=1). Sinus node dysfunction resolved after discontinuation of SOF, SMV, and amiodarone; however, reintroduction of SOF + RBV 46 days later was followed by a recurrence of the conduction abnormality. A pacemaker was implanted in this participant. Four of the 5 participants achieved sustained virologic response 12 weeks after end of treatment.

### French ANRS CO22 HEPATHER Cohort[9]

An analysis of SAEs reported in the ANRS CO22 HEPATHER cohort from August 2012 to August 2017 was conducted based on DAA exposure status. Among those exposed to

DAAs (n=10,271 person-years), 35 SAEs of arrhythmia occurred (0.3%; 34 patients were on a SOF-based regimen), and 25 of those SAEs occurred in patients whose DAA was coadministered with a cardiotropic drug. DAAs were coadministered with beta blockers only (n=10), with amiodarone + beta blocker (n=8), with amiodarone only (n=5), with amiodarone + ivabradine (n=1), or with verapamil (n=1). Four of the 25 SAEs were deemed potentially DAA related.

There was no significant difference in the incidence rate of arrhythmia between the patients who received DAAs (0.3%) and those who did not (0.3%; 95% CI: 0.75–1.96; *P*=0.47).

## Single-Center Heart and Lung Transplant Recipient Study[10]

In a single-center, retrospective clinical trial, 11 HCV-seronegative transplant recipients who received organs (lung, n=8; heart, n=3) from HCV-viremic donors began SOF/VEL treatment on postoperative Day 1, then received ≥1 dose of amiodarone a median of 1.2 days after SOF/VEL initiation. Amiodarone was given concomitantly for a median of 25 days, with a median (IQR) cumulative dose of 9086 (2195–10,952) mg. Three patients (27%) had a history of atrial fibrillation. Of the 11 patients, 7 (64%) had ≥1 bradycardic event while on concomitant SOF/VEL and amiodarone. Of these 7 patients, 5 (83%) received a concomitant beta blocker, and 6 (86%; heart recipient, n=1; lung recipient, n=5) required intervention. All bradycardic events resolved after intervention.

# Mechanism of Action of DDI Between Amiodarone and SOF-Based Regimens

The mechanism of the potential interaction between amiodarone and SOF is not known and is being studied. Several theoretical mechanisms have been proposed.[11-15]

Soriano et al proposed that amiodarone increases SOF levels via inhibition of the P-gp efflux transporter and/or that genetic predispositions associated with the liver esterase carboxylesterase-1 or the *ABCB1* gene may also increase SOF exposure due to slower conversion of SOF to its inactive metabolite, GS-331007, and impairment of P-gp transporter activity, respectively.[11]

Back et al proposed that since amiodarone is highly protein bound (96–99.9%), the addition of other highly protein-bound DAAs (LDV, >99.8%; DCV, 95.1–99.5%; SMV, >99.9%) may displace amiodarone from its binding site and rapidly increase free (active) drug concentrations, which could exacerbate the bradycardic effects of amiodarone. This hypothesis is supported by the rapid (<24 hours after start of the DAA in 6 cases) occurrence of bradycardia. Bradycardia has only been observed with amiodarone in the presence of SOF in combination with another DAA and not with high concentrations of SOF alone in doses up to 1200 mg or with SOF + RBV ± pegylated interferon.[12,13]

Millard et al provides evidence of a cardiac mechanism of action. Using the human-induced pluripotent stem cell-derived cardiomyocytes to recapitulate the SOF-amiodarone DDI in vitro, it was shown that at pharmacologically relevant concentrations, the SOF-amiodarone combination disrupted intracellular calcium handling and cellular electrophysiology. These effects were independent of other proposed mechanisms of direct ion channel block and P-gp inhibition.[14]

Lagrutta et al hypothesized a pharmacodynamic interaction between SOF and amiodarone that is dependent on the diastereochemistry of the specific drugs. When SOF (l-Ala

diastereoisomer) was coadministered with amiodarone, an increased beating rate and decreased beat amplitude was observed in pluripotent stem cell-derived cardiomyocytes both in vitro and in vivo. However, there were no alterations in rate and amplitude when MK-3682 (d-Ala diastereoisomer) was combined with amiodarone. A role of intracellular calcium and L-type calcium channel inactivation in the mechanism of action was also hypothesized.[15]

# References


1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Enclosed. Gilead Sciences Inc, HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
3. Enclosed. Gilead Sciences Inc, SOVALDI® (sofosbuvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
4. Enclosed. Gilead Sciences Inc, VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir [SOF/VEL/VOX]) tablets, for oral use. US Prescribing Information. Foster City, CA.
5. Gilead Sciences Inc. IMPORTANT DRUG WARNING Subject: Serious and Life-Threatening Cases of Symptomatic Bradycardia as well as One Case of Fatal Cardiac Arrest Reported with Coadministration of Amiodarone With Either Harvoni® (ledipasvir and sofosbuvir fixed-dose combination) or With Sovaldi® (sofosbuvir) in Combination with Another Direct Acting Antiviral. Foster City, CA2015.
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15. Lagrutta A, Regan CP, Zeng H, et al. Cardiac Drug-Drug Interaction Between HCV-NS5B Pronucleotide Inhibitors and Amiodarone is Determined By Their Specific Diastereochemistry. *Sci Rep.* 2017;7:1-13. http://www.ncbi.nlm.nih.gov/pubmed/28327633

# Abbreviations

DAA=direct-acting antiviral
DCV=daclatasvir
DDI=drug-drug interaction
LDV=ledipasvir
P-gp=P-glycoprotein
RBV=ribavirin
SAE=serious adverse event
SMV=simeprevir
SOF=sofosbuvir
VEL=velpatasvir
VOX=voxilaprevir

# Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa, Harvoni, Sovaldi, and Vosevi US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi; www.gilead.com/-/media/files/pdfs/medicines/liver-disease/harvoni/harvoni_pi; www.gilead.com/-/media/files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi; www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.

# Follow-Up

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🖱 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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