Sofosbuvir-Velpatasvir *(Epclusa)*

Drug Summary

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Class and Mechanism: Sofosbuvir-Velpatasvir (*Epclusa*) is an oral fixed-dose combination of sofosbuvir, a nucleotide analog NS5B polymerase inhibitor and velapatasvir, an NS5A replication complex inhibitor. Sofosbuvir is currently approved in the United States for the treatment of genotype 1, 2, 3 and 4 HCV infection with different regimens and durations dependent on the HCV genotype. Velpatasvir (formerly GS-5816) is a novel NS5A inhibitor that has potent in vitro anti-HCV activity across all genotypes at the picomolar level. The combination of sofosbuvir-velpatasvir is the first once-daily single-tablet regimen with pangenotypic activity.

Manufacturer for United States: Sofosbuvir-velpatasvir (*Epclusa*) (Figure 1) is manufactured by Gilead Sciences.

FDA Status: On June 28, 2016, the fixed-dose combination sofosbuvir-velpatasvir was approved by the United States FDA for the treatment of chronic hepatitis C genotypes 1-6 infection in adults.

Indications: The fixed-dose combination sofosbuvir-velpatasvir (400 mg/100 mg) is FDA-approved for the treatment of chronic hepatitis C genotypes 1 to 6 for the following patient populations:

- Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A): sofosbuvir-velpatasvir for 12 weeks
- Patients with decompensated cirrhosis (Child-Pugh B and C): sofosbuvir- velpatasvir plus

ribavirin for 12 weeks

Contraindications: If sofosbuvir-velpatasvir is used in combination with ribavirin, all of the contraindications that are known with ribavirin then apply to the use of the combination of sofosbuvir-velpatasvir and ribavirin.

Dosing: Sofosbuvir-velpatasvir is available as a coformulated, once-daily single-pill combination (Figure 2) of sofosbuvir 400 mg and velpatasvir 100 mg. The recommended dose is one tablet once daily, taken with or without food.

- Renal Impairment: For patients with mild to moderate renal impairment, no dosage adjustment of sofosbuvir-velpatasvir is recommended. There are insufficient data regarding the safety and efficacy of sofosbuvir-velpatasvir in patients with severe renal impairment (eGFR less than 30 ml/min/1.73m^2) or end-stage renal disease requiring hemodialysis. Accordingly, no dosage recommendation has been given for patients with severe renal impairment or end-stage renal disease requiring dialysis.
- Hepatic Impairment: For patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C), no dosage adjustment for sofosbuvir-velpatasvir is recommended. For patients with decompensated cirrhosis who are receiving sofosbuvir-velpatasvir and ribavirin, clinical and laboratory monitoring is recommended.

Clinical Use: The combination of sofosbuvir-velpatasvir has primarily been studied as an all-oral (interferon-free) combination regimen in treatment-naive and treatment-experienced patients with genotype 1, 2, 3, 4, and 6 chronic HCV infection. The ASTRAL phase 3 trial series demonstrated SVR12 rates ranging from 95% to 100% with sofosbuvir-velpatasvir, with or without ribavirin, typically given for 12 weeks. Sofosbuvir-velpatasvir has been shown to have efficacy in HIV-HCV coinfected patients comparable to that seen in HCV-monoinfected patients. The ASTRAL-4 trial confirmed its safety and efficacy in patients with decompensated liver disease (Child B or C cirrhosis), although the results suggested use of ribavirin would be necessary, particularly in those with genotype 3 infection.

Cost and Medication Access: The wholesale acquisition cost (WAC) for sofosbuvir-velpatasvir is $890 per pill; the cost of 12-week course of therapy is $74,760.

Adverse Effects: The most common adverse effects, observed in at least 10% of phase 3 trial participants, were headache and fatigue.

Major Drug Interactions: Sofosbuvir and velpatasvir are substrates for the drug transporter P-gp and BRCP. Thus, use of sofosbuvir-velpatasvir is not recommended with drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, since these combinations may result in significant lowering of plasma levels of sofosbuvir and velpatasvir. In addition, velpatasvir is an inhibitor of drug transporters OATP1B1, OATP1B3, OATP2B1, P-gp, and breast cancer resistance protein (BCRP). Note that velpatasvir solubility decreases as gastric pH increases and medications that raise gastric pH

will likely decrease concentrations of velpatasvir; the coadministration of proton pump inhibitors with sofosbuvir-velpatasvir is not recommended. Detailed information on drug-drug interactions that may occur with sofosbuvir-velpatasvir and other medications is provided in the sofosbuvir-velpatasvir (*Epclusa*) Full Prescribing Information.

Resistance: Due to the small number of patients with virologic failure in phase 3 trials, limited clinical data are available related to sofosbuvir-velpatasvir resistance. For two patients with genotype 1 and virologic failure, one developed a NS5A substitution Y93N and the other had a NS5A Y93H in combination with the low-level mutations K24M/T and L31I/V. Among 10 patients with genotype 3 and virologic failure, all developed a Y93H.

Full Prescribing Information: Sofosbuvir-velpatasvir (*Epclusa*) Full Prescribing Information.

Summary: Sofosbuvir-velpatasvir is the first available pangenotypic NS5A-NS5B inhibitor single-pill combination regimen, and is highly efficacious across HCV genotypes 1 to 6. It provides a much-needed interferon-free option for patients with genotype 3 infection that is more economical than sofosbuvir plus daclatasvir, and in patients who have compensated cirrhosis with genotype 3, this single-pill option provides an important ribavirin-free combination that will prove a welcome alternative to what has been available to date. Notably, unlike ledipasvir-sofosbuvir, an abbreviated duration of 8 weeks has not been studied with sofosbuvir-velpatasvir for any of the genotypes, except in conjunction with a third agent (GS-9857, an investigational pangenotypic HCV protease inhibitor). Sofosbuvir-velpatasvir, like ledipasvir-sofosbuvir, will be susceptible to drug interactions with acid-reducing agents particularly proton-pump inhibitors and the impact of these agents on real-world clinical effectiveness remains to be determined.

Clinical Trials

ASTRAL-1

In this randomized, placebo-controlled phase 3 trial, treatment-naive and treatment-experienced patients with chronic hepatitis C genotype 1, 2, 4, 5, or 6 infection were randomized in a 5:1 ratio to receive either sofosbuvir-velpatasvir or placebo. In the treatment arm (n=624), 32% had compensated cirrhotic and 19% were treatment-experienced (except for prior NS5A or NS5B experience). The overall SVR12 rate was 99%, with a range of 97 to 100% across the genotypes. Only two viral relapses occurred and these involved patients with genotype 1a and 1b. Among the 121 patients with cirrhosis, 99% achieved an SVR 12. The presence of baseline NS5A resistance-associated variants, present in 42% of evaluated patients, did not appear to influence SVR12. There was no significant difference in the rate of adverse events between the treatment and placebo arms.

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ASTRAL-2

This was a randomized, open-label phase 3 trial that compared the safety and efficacy of the fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks with sofosbuvir plus ribavirin for 12 weeks in patients with chronic HCV genotype 2 infection, including treatment-naïve and treatment-experienced patients. Patients with compensated cirrhosis were permitted and comprised 14% of the total 266 patients enrolled in the study. The SVR12 rate among sofosbuvir-velpatasvir recipients was 99% and was superior to the SVR12 rate of 94% among those who received sofosbuvir plus ribavirin, P-value=0.02. The single patient who did not achieve SVR12 in the sofosbuvir-velpatasvir group had received only one dose of the drug and discontinued after experiencing headache and anxiety. The incidence of serious adverse events was low (1%) and not different between treatment arms. The investigators concluded the sofosbuvir-velpatasvir regimen was superior to the standard regimen of sofosbuvir plus ribavirin in patients with chronic HCV genotype 2 infection. This trial (ASTRAL-2) was published in tandem with the similar trial involving patients with genotype 3 infection (ASTRAL-3).

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ASTRAL-3

In this randomized, open-label phase 3 trial, investigators compared the efficacy of the fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks with sofosbuvir plus ribavirin for 24 weeks in patients with genotype 3 HCV infection. Of the 552 patients enrolled in the study, 30% had compensated cirrhosis and 26% were treatment-experienced. The overall SVR12 rate was 95% in the sofosbuvir-velpatasvir arm and 80% in the sofosbuvir plus ribavirin arm (P-value<0.001). Among those patients with cirrhosis who received sofosbuvir-velpatasvir, the SVR12 rate were 93% for treatment-naïve and 89% for treatment-experienced patients. Among the 274 patients screened for baseline NS5A resistance-associated variants, the SVR12 rate was 88% for the 43 patients who had variants compared with 97% among those who did not.The investigators concluded the 12-week regimen of sofosbuvir-velpatasvir regimen was superior to the standard 24-week regimen of sofosbuvir plus ribavirin in patients with chronic HCV genotype 3 infection. The most substantial differences occurred in treatment experienced patients with those with cirrhosis. This trial (ASTRAL-3) was published in tandem with the similar trial involving patients with genotype 2 infection (ASTRAL-2).

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ASTRAL-4

The ASTRAL-4 trial was a randomized, open-label phase 3 trial designed to examine the safety and efficacy of the fixed-dose combination of sofosbuvir-velpatasvir with or without ribavirin in patients with genotype 1, 2, 3, 4, or 6 chronic HCV infection and decompensated cirrhosis. Treatment-naïve and treatment-experienced patients with Child-Pugh-Turcotte (CTP) class B disease were randomized to one of three arms: (1) sofosbuvir-velpatasvir for 12 weeks (n=90), (2) sofosbuvir-velpatasvir plus ribavirin for 12 weeks (n=87), or (3) sofosbuvir-velpatasvir for 24 weeks (n=90). All three regimens were highly efficacious among genotype 1 patients (88%, 96%, and 92% respectively) and genotypes 2, 4 and 6 patients (100%, 100%, and 86% respectively). Notably among patients with genotype 3, the treatment groups without ribavirin had lower SVR12 rates of 50% (each) compared with 85% in the sofosbuvir-velpatasvir plus ribavirin arm. Overall, the CTP scores improved over baseline in 47%, remained unchanged in 42%, and worsened in 11%. A total of 22 patients experienced virologic failure; most (n=18) had NS5A variants at the time of failure with the Y93H/N occurring most frequently.

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ASTRAL-5

The ASTRAL-5 study was a single-arm, open-label phase 3 trial of sofosbuvir-velpatasvir for 12 weeks in patients with HIV and HCV coinfection. The study enrolled 106 patients with genotype 1, 2, 3, 4 or 6 HCV infection; 18% had compensated cirrhosis and 29% were treatment-experienced. The mean CD4 count was 583 cells/mm^3 and all patients had HIV viral suppression. A variety of antiretroviral regimens, including tenofovir disoproxil fumarate (DF) and boosting agents (cobicistat or ritonavir), were permitted. The overall SVR12 rate was 95%; two viral relapses occurred, both in the genotype 1a subgroup. The presence of cirrhosis or treatment experience did not appear to influence treatment response. Creatinine clearance was lower among people taking boosted versus unboosted tenofovir DF, and lowest among people not taking tenofovir DF (who may have had existing kidney problems), but it remained relatively stable over time in all groups. No patient experienced HIV viral rebound on HCV treatment.

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Figures

Figure 1 Sofosbuvir-Velpatasvir (*Epclusa*) Bottle

Photo: Andrew Karpenko, University of Washington

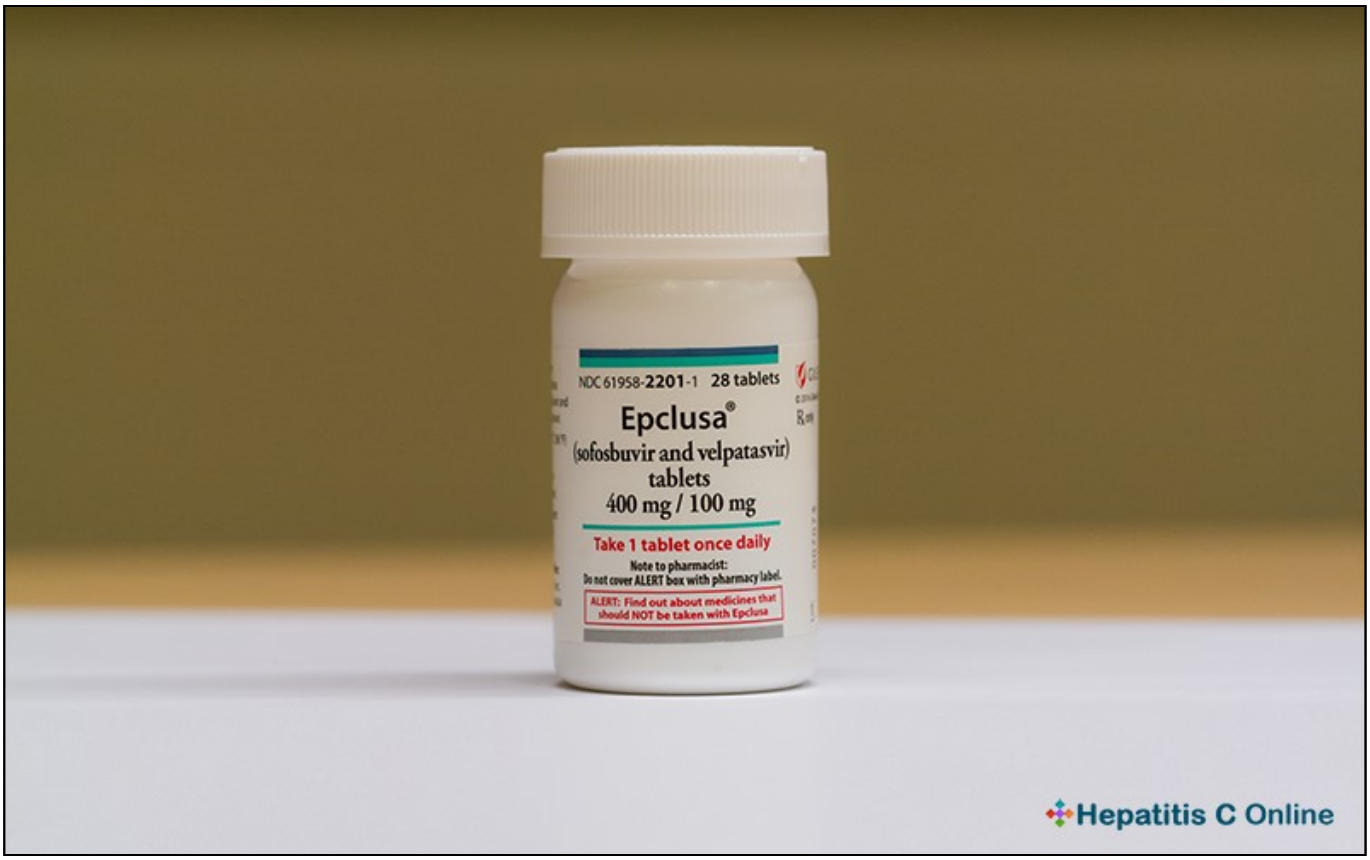
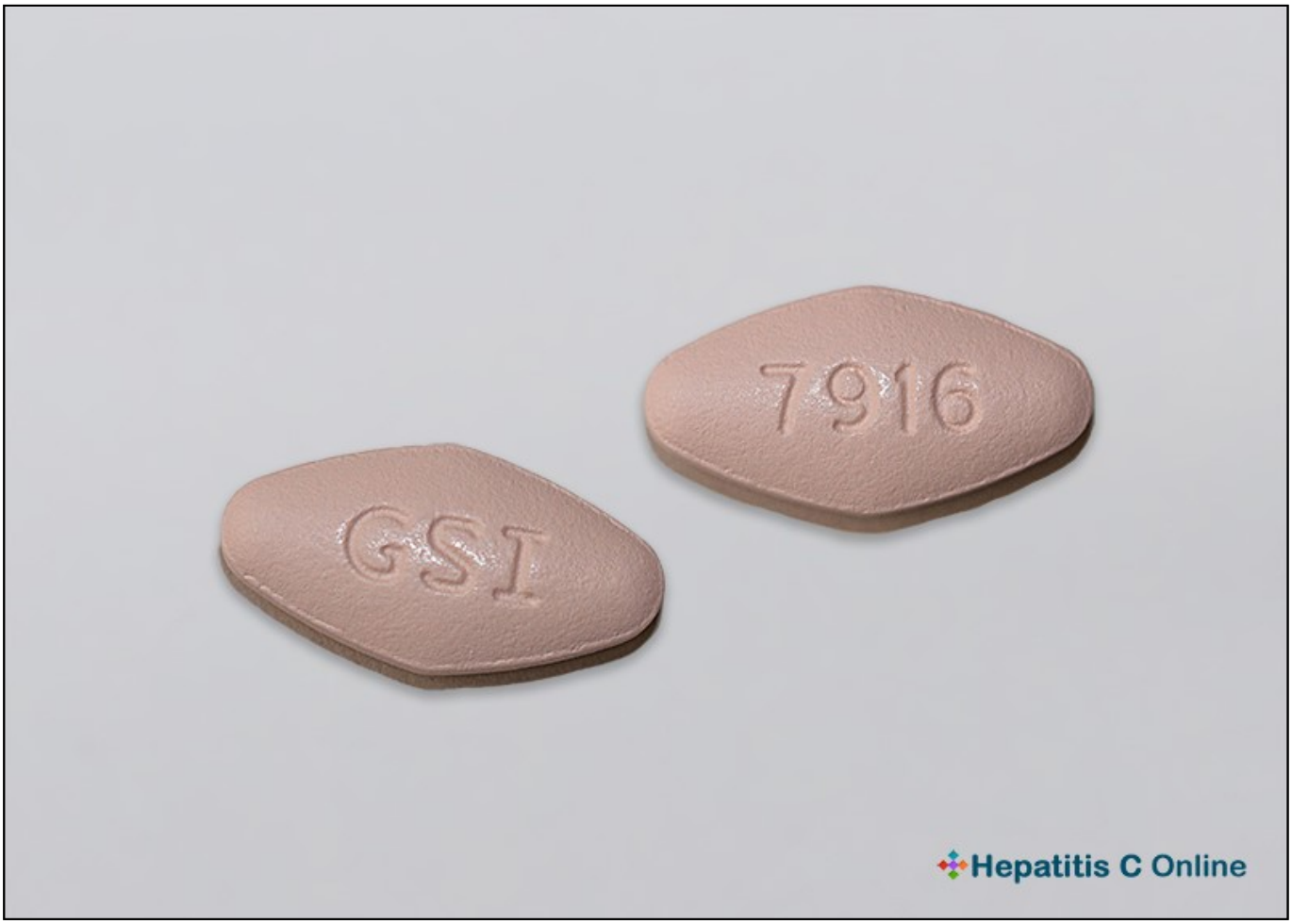


Figure 2 Sofosbuvir-Velpatasvir (*Epclusa*) Tablets

Photo: Andrew Karpenko, University of Washington



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