Sofosbuvir-Velpatasvir (*Epclusa*)

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**Drug Summary**

Sofosbuvir-velpatasvir is a pangenotypic NS5A-NS5B inhibitor single-pill combination regimen that has potent activity against hepatitis C virus (HCV) genotypes 1, 2, 3, 4, 5, and 6. It provides a much-needed option for patients with HCV genotype 3 infection, including those with compensated cirrhosis. Notably, 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 (voxilaprevir). Sofosbuvir-velpatasvir, like ledipasvir-sofosbuvir, may have have levels significantly reduced with acid-reducing agents, particularly proton-pump inhibitors.

**Adverse Effects**

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

**Class and Mechanism**

Sofosbuvir-Velpatasvir 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

*Epclusa* (ep-KLOO-suh) is a fixed dose combination of sofosbuvir and velpatasvir (*Figure 1*). It 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/1.73m²) 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.

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.

Key Drug Interactions

For complete information on sofosbuvir-velpatasvir-related drug interactions, see the Drug Interactions section in the Sofosbuvir-Velpatasvir (Epclusa) Prescribing Information.
Full Prescribing Information
Sofosbuvir-velpatasvir (Epclusa) Full Prescribing Information.