Sofosbuvir and Velpatasvir
(Systemic)

HCV antiviral; fixed combination containing sofosbuvir (nucleotide analog HCV NS5B polymerase inhibitor) and velpatasvir (HCV NS5A replication complex inhibitor [NS5A inhibitor]).

Class: B:18.40.16 • HCV Polymerase Inhibitors (AHFS primary)
Brands: Epclusa®

Uses

Chronic HCV Infection
- Treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection in treatment-naïve (previously untreated) or previously treated adults, including those with cirrhosis (compensated or decompensated).
- Used alone or in conjunction with ribavirin, depending on certain patient factors (e.g., presence of decompensated cirrhosis).
- Treatment of chronic HCV infection is complex and rapidly evolving; consult a specialist to obtain the most up-to-date information. Information from the American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), and International Antiviral Society–USA (IAS–USA) regarding diagnosis and management of HCV infection, including recommendations for initial treatment, is available at http://www.hcvguidelines.org.

Dosage and Administration

General
- For treatment of chronic HCV infection, sofosbuvir/velpatasvir is used alone or in conjunction with ribavirin.
- Base specific regimen on certain patient factors (e.g., presence of decompensated cirrhosis).
- Screen all patients for evidence of HBV infection prior to initiating sofosbuvir/velpatasvir. (See Risk of HBV Reactivation in Patients Coinfected with HCV and HBV under Cautions.)

Administration

Oral Administration
- Administer orally once daily without regard to food.

Dosage
- Available as fixed-combination tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir.

Adults

Treatment of Chronic HCV Infection
- >HCV Genotype 1, 2, 3, 4, 5, or 6 Infection
  - Oral: 1 tablet (sofosbuvir 400 mg and velpatasvir 100 mg) once daily.
  - Noncirrhotic or with compensated cirrhosis (Child-Pugh class A): Use alone for a duration of 12 weeks.
  - Decompensated cirrhosis (Child-Pugh class B or C): Use in conjunction with ribavirin for a duration of 12 weeks.

Special Populations

Hepatic Impairment
- Mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C): Dosage adjustments not needed. (See Hepatic Impairment under Cautions.)
- Adults with decompensated cirrhosis (Child-Pugh class B or C): Use usual dosage of sofosbuvir/velpatasvir in conjunction with ribavirin for treatment of HCV genotype 1, 2, 3, 4, 5, or 6 infection. Some experts suggest sofosbuvir/velpatasvir can be used alone (without ribavirin) for treatment of HCV genotype 5 or 6 infection, regardless of cirrhosis status.

Renal Impairment
- Mild or moderate renal impairment: Dosage adjustments not needed.
- Severe renal impairment (estimated GFR <30 mL/minute per 1.73 m²) or end-stage renal disease (ESRD): Dosage recommendations not available; safety and efficacy not established in such patients. (See Renal Impairment under Cautions.)

Geriatric Patients
- Dosage adjustments not needed.

Cautions

Contraindications
- If sofosbuvir/velpatasvir used in conjunction with ribavirin, the contraindications to ribavirin also apply. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)

Warnings/Precautions

Warnings
- Risk of HBV Reactivation in Patients Coinfected with HCV and HBV
  - Postmarketing reports of reactivation of HBV infection when direct-acting antivirals (DAAs) were used for treatment of HCV infection in patients with HBV coinfection; fulminant hepatitis, hepatic failure, and death reported in some cases.

  - HBV reactivation (defined as abrupt increase in HBV replication manifested as rapid increase in serum HBV DNA levels or detection of hepatitis B surface antigen [HBsAg] in an individual who was previously HBsAg negative and hepatitis B core antibody [anti-HBc] positive) reported in patients with HCV and HBV coinfection receiving HCV treatment with a regimen that included HCV DAAs without interferon alfa. HBV reactivation usually occurred within 4–8 weeks after initiation of HCV treatment. Patients with HBV reactivation have been heterogeneous in terms of HCV genotype and in terms of baseline HBV disease. While some patients with HBV reactivation were HBsAg positive, others had serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive).

  - Mechanism for HBV reactivation in coinfected patients receiving HCV DAAs unknown. Although HCV DAAs not known to cause immunosuppression, HBV reactivation in coinfected patients may result from a complex interplay of host immunologic responses in the setting of infection with 2 hepatitis viruses.

  - Prior to initiating treatment with an HCV DAA, including sofosbuvir/velpatasvir, screen all patients for evidence of current or prior HBV infection by measuring HBsAg, anti-HBs, and anti-HBc. If there is serologic evidence of HBV infection, measure baseline HBV DNA level. In all patients with evidence of current or prior HBV infection, monitor for clinical and laboratory signs (i.e., HBsAg, HBV DNA levels, serum aminotransferase concentrations, bilirubin concentrations) of hepatitis flare or HBV reactivation during and after treatment with HCV DAAs. If appropriate, initiation of HBV treatment may be warranted.

  - Advise patients with HCV and HBV coinfection receiving sofosbuvir/velpatasvir to immediately contact a clinician if they develop any signs or symptoms of serious liver injury (e.g., fatigue, weakness, loss of appetite, nausea and vomiting, yellowing of the eyes or skin, light-colored bowel movements).

  - When making decisions regarding HBV monitoring or HBV treatment in coinfected patients, consult a clinician with expertise in managing HBV infection.

Other Warnings/Precautions

Cardiovascular Effects
- Postmarketing reports of symptomatic bradycardia, including cases requiring pacemaker intervention, in patients receiving amiodarone concomitantly with HCV treatment regimen containing sofosbuvir in conjunction with another HCV DAA (e.g., daclatasvir, ledipasvir, simeprevir). Fatal cardiac arrest reported in one patient receiving fixed combination of ledipasvir and sofosbuvir (ledipasvir/sofosbuvir).

  - In most reported cases, bradycardia occurred within hours to days after HCV treatment initiated in patients receiving amiodarone (also has been observed up to 2 weeks after initiation of HCV treatment) and resolved after HCV treatment discontinued. Mechanism for this adverse cardiovascular effect unknown.

  - Patients who may be at increased risk for symptomatic bradycardia if amiodarone used concomitantly with sofosbuvir/velpatasvir include those also receiving a β-adrenergic blocking agent, those with underlying cardiac comorbidities, and/or those with advanced liver disease.

  - Concomitant use of amiodarone with sofosbuvir/velpatasvir not recommended.

  - If there are no alternative HCV treatment options and regimen of sofosbuvir/velpatasvir must be used in a patient receiving amiodarone, advise patient about the risk of serious bradycardia before initiating HCV treatment. Perform cardiac monitoring in an inpatient setting during first 48 hours of concomitant use of amiodarone and sofosbuvir/velpatasvir; heart rate monitoring should then be performed daily (outpatient or self-monitoring) through at least the first 2 weeks of concomitant use. Similar cardiac monitoring recommended in patients who discontinued amiodarone just prior to initiation of sofosbuvir/velpatasvir or if there are no other treatment options and amiodarone must be initiated in a patient already receiving sofosbuvir/velpatasvir.

  - Advise patients receiving amiodarone concomitantly with sofosbuvir/velpatasvir to immediately contact a clinician if signs or symptoms of bradycardia (e.g., near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion, memory problems) develop.

Interactions
- Concomitant use of sofosbuvir/velpatasvir and inducers of the P-glycoprotein (P-gp) transport system and/or moderate to potent inducers of CYP2B6, 2C8, or 3A4 (e.g.,
Velpatasvir inhibits OATP1B1, 1B3, and 2B1.

When used in conjunction with ribavirin, consider that ribavirin may cause fetal toxicity and/or death. Extreme care must be taken to avoid pregnancy in female patients and female partners of male patients receiving a ribavirin-containing regimen. Obtain a negative pregnancy test for female patients of childbearing potential immediately prior to initiating ribavirin; perform pregnancy tests monthly during and for 6 months after ribavirin treatment is completed. Women of childbearing potential (and their male partners) must use at least 2 forms of effective contraception during and for 6 months after ribavirin treatment is completed.

**Specific Populations**

**Pregnancy**

Adequate data not available regarding use in pregnant women. In animal studies, no evidence that sofosbuvir or velpatasvir affected fetal development at dosages tested.

When used in conjunction with ribavirin, consider that ribavirin is contraindicated in pregnant women and male partners of pregnant women. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)

**Lactation**

Not known whether sofosbuvir/velpatasvir and metabolites distributed into human milk.

Predominant metabolite of sofosbuvir (GS-331007) distributed into milk in rats; velpatasvir distributed into milk in rats and detected in plasma of suckling rat pups. GS-331007 and velpatasvir had no apparent effects on nursing pups.

Consider benefits of breast-feeding and importance of the drug to the woman; also consider potential adverse effects on the breast-fed child from the drug or underlying maternal condition.

When used in conjunction with ribavirin, consider potential for adverse reactions to ribavirin in nursing infants and discontinue nursing or the ribavirin-containing regimen. (See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)

**Pediatric Use**

Safety and efficacy not established in pediatric patients <18 years of age.

**Geriatric Use**

No overall differences in safety and efficacy in patients ≥65 years of age compared with younger adults, but increased sensitivity in some older individuals cannot be ruled out.

**Hepatic Impairment**

HCV-infected individuals with moderate or severe hepatic impairment (Child-Pugh class B or C). Increased sofosbuvir and GS-331007 exposures compared with those in individuals with normal hepatic function.

Moderate or severe hepatic impairment (Child-Pugh class B or C) without HCV infection: Velpatasvir exposure similar to exposure in individuals with normal hepatic function.

When velpatasvir/sofosbuvir is used in conjunction with ribavirin in patients with decompensated cirrhosis (Child-Pugh class B or C), clinical and hepatic laboratory monitoring is recommended as clinically indicated.

**Renal Impairment**

Mild, moderate, or severe renal impairment without HCV infection: Increased sofosbuvir and GS-331007 exposures compared with those in individuals with normal renal function.

ESRD without HCV infection: Increased sofosbuvir and GS-331007 exposures when administered 1 hour before or 1 hour after hemodialysis compared with exposures in individuals with normal renal function.

Severe renal impairment without HCV infection: Velpatasvir exposure similar to exposure in healthy individuals.

**Common Adverse Effects**

Sofosbuvir/velpatasvir in patients without cirrhosis or with compensated cirrhosis: Headache, fatigue, nasopharyngitis, nausea, insomnia.

Sofosbuvir/velpatasvir in conjunction with ribavirin in patients with decompensated cirrhosis: Fatigue, anemia, nausea, headache, insomnia, diarrhea, muscle spasm, dyspnea, cough.

The following drug interactions are based on studies using sofosbuvir/velpatasvir, sofosbuvir alone, or velpatasvir alone, or are predicted to occur. When sofosbuvir/velpatasvir used, consider interactions associated with both drugs in the fixed combination.

**Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes**

Moderate or potent CYP2B6, 2C8, or 3A4 inducers: Possible decreased sofosbuvir and/or velpatasvir plasma concentrations leading to reduced therapeutic effect; concomitant use of sofosbuvir/velpatasvir with such inducers not recommended.

CYP2B6, 2C8, or 3A4 inhibitors: Possible increased velpatasvir plasma concentrations; sofosbuvir/velpatasvir may be used concomitantly with such inhibitors.

**Drugs Affecting or Affected by P-glycoprotein Transport System**

P-gp substrates: Intestinal absorption may be affected resulting in increased exposure of such substrates.

P-gp inducers: Possible decreased sofosbuvir and/or velpatasvir plasma concentrations leading to reduced therapeutic effect; concomitant use of sofosbuvir/velpatasvir with P-gp inducers not recommended.

P-gp inhibitors: Possible increased sofosbuvir and/or velpatasvir concentrations; sofosbuvir/velpatasvir may be used concomitantly with P-gp inhibitors.

**Drugs Affecting or Affected by Breast Cancer Resistance Protein**

BCRP substrates: Intestinal absorption may be affected resulting in increased exposure of such substrates.

BCRP inhibitors: Possible increased sofosbuvir and/or velpatasvir concentrations; sofosbuvir/velpatasvir may be used concomitantly with BCRP inhibitors.

**Drugs Affecting or Affected by Organic Anion Transporting Polypeptides**

OATP1B1, 1B3, or 2B1 substrates: Intestinal absorption may be affected resulting in increased exposure of such substrates.

**Specific Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids (aluminum and magnesium hydroxides)</td>
<td>Decreased velpatasvir concentrations expected; increased gastric pH decreases velpatasvir solubility</td>
<td>Take antacids 4 hours before or after sofosbuvir/velpatasvir</td>
</tr>
<tr>
<td>Antiarrhythmic agents (amiodarone)</td>
<td>Amiodarone: Concomitant use with sofosbuvir/velpatasvir may result in serious symptomatic bradycardia; effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown</td>
<td>Amiodarone: Concomitant use with sofosbuvir/velpatasvir not recommended; if concomitant use necessary, patient counseling and cardiac monitoring required (see Cardiovascular Effects under Cautions)</td>
</tr>
<tr>
<td>Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: Decreased sofosbuvir and velpatasvir concentrations expected</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: Concomitant use with sofosbuvir/velpatasvir not recommended</td>
</tr>
<tr>
<td>Antifungals, azoles (ketoconazole)</td>
<td>Ketoconazole: No clinically important pharmacokinetic interactions with velpatasvir</td>
<td></td>
</tr>
<tr>
<td>Antimycobacterial agents (rifabutin, rifampin, rifapentine)</td>
<td>Rifabutin, rifampin: Decreased sofosbuvir and velpatasvir concentrations expected</td>
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<tr>
<td>Atazanavir</td>
<td>Rifabutin, rifampin, rifapentine: Concomitant use with sofosbuvir/velpatasvir not recommended</td>
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The following drug interactions are based on studies using sofosbuvir/velpatasvir, sofosbuvir alone, or velpatasvir alone, or are predicted to occur. When sofosbuvir/velpatasvir used, consider interactions associated with both drugs in the fixed combination.

**Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes**

Moderate or potent CYP2B6, 2C8, or 3A4 inducers: Possible decreased sofosbuvir and/or velpatasvir plasma concentrations leading to reduced therapeutic effect; concomitant use of sofosbuvir/velpatasvir with such inducers not recommended.

CYP2B6, 2C8, or 3A4 inhibitors: Possible increased velpatasvir plasma concentrations; sofosbuvir/velpatasvir may be used concomitantly with such inhibitors.

**Drugs Affecting or Affected by P-glycoprotein Transport System**

P-gp substrates: Intestinal absorption may be affected resulting in increased exposure of such substrates.

P-gp inducers: Possible decreased sofosbuvir and/or velpatasvir plasma concentrations leading to reduced therapeutic effect; concomitant use of sofosbuvir/velpatasvir with P-gp inducers not recommended.

P-gp inhibitors: Possible increased sofosbuvir and/or velpatasvir concentrations; sofosbuvir/velpatasvir may be used concomitantly with P-gp inhibitors.

**Drugs Affecting or Affected by Breast Cancer Resistance Protein**

BCRP substrates: Intestinal absorption may be affected resulting in increased exposure of such substrates.

BCRP inhibitors: Possible increased sofosbuvir and/or velpatasvir concentrations; sofosbuvir/velpatasvir may be used concomitantly with BCRP inhibitors.

**Drugs Affecting or Affected by Organic Anion Transporting Polypeptides**

OATP1B1, 1B3, or 2B1 substrates: Intestinal absorption may be affected resulting in increased exposure of such substrates.

**Specific Drugs**

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<td>Decreased velpatasvir concentrations expected; increased gastric pH decreases velpatasvir solubility</td>
<td>Take antacids 4 hours before or after sofosbuvir/velpatasvir</td>
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<td>Antiarrhythmic agents (amiodarone)</td>
<td>Amiodarone: Concomitant use with sofosbuvir/velpatasvir may result in serious symptomatic bradycardia; effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown</td>
<td>Amiodarone: Concomitant use with sofosbuvir/velpatasvir not recommended; if concomitant use necessary, patient counseling and cardiac monitoring required (see Cardiovascular Effects under Cautions)</td>
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<td>Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: Decreased sofosbuvir and velpatasvir concentrations expected</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: Concomitant use with sofosbuvir/velpatasvir not recommended</td>
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<td>Rifabutin, rifampin, rifapentine: Concomitant use with sofosbuvir/velpatasvir not recommended</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Rifabutin, rifampin, rifapentine: Concomitant use with sofosbuvir/velpatasvir not recommended</td>
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</table>

In vitro studies indicate slow metabolic turnover of velpatasvir by CYP2B6, 2C8, and 3A4. Velpatasvir inhibits P-gp transport system; sofosbuvir and velpatasvir are substrates of P-gp. Velpatasvir inhibits breast cancer resistance protein (BCRP); sofosbuvir and velpatasvir are substrates of BCRP.

Velpatasvir transported by organic anion transporting polypeptide (OATP) 1B1 and 1B3; velpatasvir inhibits OATP1B1, 1B3, and 2B1.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetic Interactions</th>
<th>HIV Antiretroviral Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Darunavir</strong></td>
<td><strong>Ritonavir-boosted darunavir:</strong> No clinically important pharmacokinetic interactions</td>
<td>HIV antiretroviral regimen of ritonavir-boosted darunavir in conjunction with fixed combination of emtricitabine and tenofovir disoproxil fumarate (emtricitabine/tenofovir DF): Increased velpatasvir and tenofovir concentrations and AUC</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>Increased digoxin concentrations and AUC when used concomitantly with velpatasvir</td>
<td>HIV antiretroviral regimens that include <em>ritonavir-boosted darunavir and tenofovir DF</em>: Monitor for tenofovir-associated adverse effects</td>
</tr>
<tr>
<td><strong>Dolutegravir</strong></td>
<td>No clinically important pharmacokinetic interactions with sofosbuvir/velpatasvir</td>
<td>HIV antiretroviral regimen of ritonavir-boosted darunavir in conjunction with emtricitabine/tenofovir DF: Decreased sofosbuvir and velpatasvir concentrations and AUC; increased tenofovir concentrations and AUC</td>
</tr>
<tr>
<td><strong>Efavirenz</strong></td>
<td>Fixed combination of efavirenz, emtricitabine, and tenofovir DF (efavirenz/emtricitabine/tenofovir DF): No clinically important effect on sofosbuvir pharmacokinetics; decreased velpatasvir concentrations and AUC; increased tenofovir concentrations and AUC</td>
<td>HIV antiretroviral regimens containing efavirenz: Concomitant use with sofosbuvir/velpatasvir not recommended</td>
</tr>
<tr>
<td><strong>Elvitegravir</strong></td>
<td>Fixed combination of elvitegravir, cobicistat, emtricitabine, and tenofovir DF (EVG/c/FTC/TDF): No clinically important effect on sofosbuvir, velpatasvir, elvitegravir, cobicistat, or emtricitabine pharmacokinetics; increased tenofovir concentrations and AUC</td>
<td>EVG/c/FTC/TDF: Monitor for tenofovir-associated adverse effects</td>
</tr>
</tbody>
</table>

**Emtricitabine**
- No clinically important pharmacokinetic interactions with sofosbuvir/velpatasvir

**Estrogens/progestins**
- Oral contraceptive containing ethinyl estradiol and norgestimate: No clinically important effects on pharmacokinetics of ethinyl estradiol or norgestimate and its active metabolites (norelgestromin, norgestimate)

**Histamine H₂-receptor antagonists**
- Decreased velpatasvir concentrations expected; increased gastric pH decreases velpatasvir solubility
- Administer H₂-antagonists concurrently with or 12 hours apart from sofosbuvir/velpatasvir; do not exceed H₂-antagonist dosages comparable to famotidine 40 mg twice daily

**HMG-CoA reductase inhibitors (statins)**
- Atorvastatin: Increased atorvastatin concentrations expected; increased risk of myopathy and rhabdomyolysis
- Pravastatin: No clinically important interactions
- Rosuvastatin: Increased rosuvastatin concentrations; increased risk of myopathy and rhabdomyolysis
- Atorvastatin: Closely monitor for statin-associated adverse effects (e.g., myopathy, rhabdomyolysis)
- Rosuvastatin: Do not exceed rosuvastatin dosage of 10 mg daily

**Digoxin therapeutic concentration monitoring recommended if used concomitantly with sofosbuvir/velpatasvir**
<table>
<thead>
<tr>
<th>Drug/interaction</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John's wort</td>
<td>Possible decreased sofosbuvir and velpatasvir</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Fixed combination of lopinavir and ritonavir (lopinavir/ritonavir): No clinically important effect on sofosbuvir or velpatasvir</td>
</tr>
<tr>
<td>Methadone</td>
<td>No clinically important pharmacokinetic interactions with sofosbuvir</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>Increased topotecan concentrations expected</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>HIV antiretroviral regimens that include tenofovir DF; Monitor for tenofovir-associated adverse effects</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>No in vitro evidence of antagonistic anti-HCV effects with sofosbuvir or velpatasvir</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Fixed combination of emtricitabine, rilpivirine, and tenofovir DF (emtricitabine/rilpivirine/tenofovir DF): No clinically important effect on emtricitabine or rilpivirine pharmacokinetics; increased tenofovir concentrations and AUC</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Major route of elimination is renal clearance. Following single 400-mg oral dose, 80% eliminated in urine (mainly as GS-331007), 14% in feces, and 2.5% in expired air.</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Concomitant use with sofosbuvir/velpatasvir not recommended</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>Concomitant use with sofosbuvir/velpatasvir</td>
</tr>
<tr>
<td>Interferons</td>
<td>Interferon alfa: No in vitro evidence of antagonistic anti-HCV effects with sofosbuvir or velpatasvir</td>
</tr>
<tr>
<td>Immunosuppressants (cyclosporine, tacrolimus)</td>
<td>Cyclosporine: No clinically important pharmacokinetic interactions with sofosbuvir or velpatasvir Tacrolimus: No clinically important pharmacokinetic interactions with sofosbuvir</td>
</tr>
</tbody>
</table>

### Pharmacokinetics

#### Absorption

**Bioavailability**

Following oral administration of sofosbuvir/velpatasvir, peak plasma concentrations of sofosbuvir occur approximately 0.5–1 hour after the dose. Peak plasma concentrations and AUC of sofosbuvir and GS-331007 are similar in HCV-infected and healthy adults.

Following oral administration of sofosbuvir/velpatasvir, peak plasma concentrations of velpatasvir occur 3 hours after the dose. Peak plasma concentrations and AUC of velpatasvir are 42 and 37%, lower, respectively, in HCV-infected adults compared with healthy adults.

**Food**

Administration of sofosbuvir/velpatasvir with moderate-fat (approximately 600 kcal, 30% fat) or high-fat (approximately 800 kcal, 50% fat) meal increased sofosbuvir exposures by 60 or 78%, respectively, and increased velpatasvir exposures by 34 or 21%, respectively.

#### Special Populations

**Sofosbuvir:** In HCV-infected individuals with moderate or severe hepatic impairment (Child-Pugh class B or C), sofosbuvir AUC is 126 or 143% higher, respectively, compared with individuals with normal hepatic function; GS-331007 AUC is 18 or 9% higher, respectively.

**Velpatasvir:** In individuals with moderate or severe hepatic impairment (Child-Pugh class B or C) without HCV infection, AUC of velpatasvir after single 100-mg dose is similar to that observed in individuals with normal hepatic function.

**Sofosbuvir:** In individuals with mild, moderate, or severe renal impairment without HCV infection, sofosbuvir AUC after single 400-mg dose is 61, 107, or 171% higher, respectively, compared with individuals with normal renal function; GS-331007 AUC is 55, 88, or 451% higher, respectively.

**Velpatasvir:** In individuals with severe renal impairment without HCV infection, no clinically important differences in velpatasvir pharmacokinetics after single 100-mg dose compared with healthy individuals.

**Population pharmacokinetic analysis in HCV-infected individuals indicates cirrhosis does not substantially affect sofosbuvir, GS-331007, or velpatasvir exposures.**

**Population pharmacokinetic analysis in HCV-infected individuals indicates that gender and race do not affect sofosbuvir, GS-331007, or velpatasvir exposures.**

#### Distribution

**Plasma Protein Binding**

- **Sofosbuvir:** Approximately 61–65%.
- **Velpatasvir:** >99.5%.

#### Elimination

**Metabolism**

- **Sofosbuvir:** Prodrug that undergoes intracellular metabolic activation in the liver (hydrolysis by human cathepsin A [CatA] or carboxylesterase 1 [CES1], phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 [HINT1], and phosphorylation by pyrimidine nucleotide biosynthesis pathway). Results in formation of pharmacologically active metabolite, GS-461203. Desphosphorylation subsequently occurs leading to formation of GS-331007 (the predominant circulating metabolite); GS-331007 has no anti-HCV activity.

- **Velpatasvir:** Metabolized by CYP2B6, 2C8, and 3A4.

**Elimination Route**

- **Sofosbuvir:** Major route of elimination is renal clearance. Following single 400-mg oral dose, 80% eliminated in urine (mainly as GS-331007), 14% in feces, and 2.5% in expired air.

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Inform patients that reactivation of HBV infection has occurred in coinfected patients being treated for chronic HCV infection. Importance of taking the recommended dosage of sofosbuvir/velpatasvir for the recommended duration of treatment; importance of not missing doses. Inform patients that reactivation of HBV infection has occurred in coinfected patients being treated for chronic HCV infection. Importance of informing clinician of any history of HBV infection or other liver problems (e.g., cirrhosis). Importance of immediately contacting a clinician if any signs or symptoms of serious liver injury (e.g., fatigue, weakness, loss of appetite, nausea and vomiting, yellowing of the eyes or skin, light-colored bowel movements) occur. See Risk of HBV Reactivation in Patients Coinfected with HCV and HBV under Cautions.)

If sofosbuvir/velpatasvir is used in a patient receiving amiodarone, advise the patient about the risk of serious symptomatic bradycardia and the importance of immediately contacting a clinician if signs or symptoms of bradycardia (e.g., near-fainting or fainting, dizziness, lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion, memory problems) occur. See Cardiovascular Effects under Cautions.)

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary or herbal supplements, as well as any concomitant illnesses.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. If used in conjunction with ribavirin, advise men and women of importance of using 2 forms of effective contraception during and for 6 months after ribavirin therapy. See Precautions Related to Fixed Combinations and Multiple-drug Treatment Regimens under Cautions.)

Importance of informing patients of other important precautionary information. (See Cautions.)

Actions

- Sofosbuvir/velpatasvir is a fixed combination of 2 HCV antivirals. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor and velpatasvir is an HCV NS5A replication complex inhibitor (NS5A inhibitor).
- Sofosbuvir and velpatasvir are both DAA's with activity against HCV. No in vitro evidence of antagonistic anti-HCV effects between the drugs in HCV replicon studies.
- Sofosbuvir is a produg that undergoes metabolic activation in the liver to a pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by NS5B polymerase; acts as RNA chain terminator. In vitro studies using biochemical and cell-based replicon assays indicate that GS-461203 has activity against HCV genotypes 1b, 2a, 3a, and 4a. Sofosbuvir has shown in vitro activity against full-length or chimeric replicons of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, 5b, 5c, and 6a (mean drug concentration required to inhibit viral replication by 50% [EC50] ranges from 14–110 nM).
- Velpatasvir inhibits the HCV NS5A protein, which is required for viral replication. Velpatasvir has shown in vitro activity against full-length or chimeric replicons of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4a, 5a, and 6a (mean EC50 ranges from 0.002–0.13 nM).
- Certain amino acid substitutions in NS5B polymerase of HCV genotypes 1b, 2a, 3a, 4a, 5a, and 6a have been selected in cell culture and have been associated with reduced susceptibility to sofosbuvir in vitro in replicon studies. In all replicon genotypes tested, the S282T substitution was associated with reduced susceptibility to sofosbuvir; in genotypes 2a, 5, and 6 replicons, an M289L substitution developed along with the S282T substitution. Treatment-emergent NS5B resistance-associated substitutions were detected in phase 3 clinical trials evaluating sofosbuvir/velpatasvir in patients with HCV genotype 3a infection (e.g., L314F, L314I, L314P) who experienced virologic failure.
- Certain amino acid substitutions in NS5A of HCV genotype 1a (e.g., L31V, Y93H/N), genotype 1b (e.g., L31V, Y93H), genotype 2a (e.g., F28S, Y93H), genotype 3a (e.g., Y93H/S), genotype 4a (e.g., Y93H), and genotype 6 (e.g., L31V, P52AL/QR) have been selected in cell culture and have been associated with reduced susceptibility to velpatasvir in vitro in replicon studies. Combinations of these NS5A substitutions often resulted in greater reductions in susceptibility to velpatasvir compared with a single NS5A substitution. Treatment-emergent NS5A resistance-associated substitutions were detected in phase 3 clinical trials evaluating sofosbuvir/velpatasvir in patients with HCV genotype 1a (e.g., Y93N, Q30R, H58D), genotype 1b (e.g., L31MV, Y93H), genotype 1c (e.g., Y93H, K24MT, L31IV), or genotype 3a (e.g., Y93H, M281V, S38P/L, P58L, A30V, H58T) infection who experienced virologic failure. Some of these patients also had baseline NS5A polymorphisms at resistance-associated amino acid positions.
- Sofosbuvir and velpatasvir are active against HCV with substitutions associated with resistance to other HCV DAA's with different mechanisms of action (e.g., HCV NS5B polymerase inhibitors, HCV NS3 protease inhibitors). Efficacy of sofosbuvir/velpatasvir not established in patients in whom previous treatment with a regimen that included an HCV NS5A inhibitor failed.

Advice to Patients

- Importance of reading patient information provided by the manufacturer.
- Advise patients to take sofosbuvir/velpatasvir once daily (with or without food) on a regular dosing schedule.
- Importance of taking the recommended dosage of sofosbuvir/velpatasvir for the recommended duration of treatment; importance of not missing doses.

Preparations

Expiocin in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

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<th>Sofosbuvir and Velpatasvir</th>
<th>Oral Tablets, film-coated</th>
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<tr>
<td>Sofosbuvir 400 mg and Velpatasvir 100 mg</td>
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