# Sofosbuvir/Velpatasvir (Epclusa®)

## National Drug Monograph

## August 2016

**VA Pharmacy Benefits Management Services, Medical Advisory Panel,**
**VISN Pharmacist Executives and Office of Public Health**

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

## FDA Approval Information[1]

| | |
|---|---|
| **Description/ Mechanism of Action** | Sofosbuvir/velpatasvir is a fixed-dose combination of two direct acting antivirals that have different mechanisms of action. Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor while velpatasvir is a NS5A inhibitor. |
| **Indication(s) under Review in this document** | Sofosbuvir/velpatasvir is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection. |
| **Dosage Form(s) Under Review** | Fixed-dose combination tablet containing 400 mg of sofosbuvir and 100mg velpatasvir. |
| **REMS** | NO REMS |
| **Pregnancy Rating** | - If sofosbuvir/velpatasvir is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant.<br>- If sofosbuvir/velpatasvir is administered without ribavirin, no adequate human data are available to establish whether or not it poses a risk to pregnancy outcomes. |

## Executive Summary[1]

| | |
|---|---|
| Efficacy | • Sofosbuvir/velpatasvir (SOF/VEL) was evaluated in four Phase 3 randomized, studies conducted in patients with HCV genotypes 1 through 6 with or without compensated cirrhosis and in patients with decompensated (Childs-Pugh B) cirrhosis. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment. In compensated cirrhosis, sofosbuvir/velpatasvir for 12 weeks achieved SVRs in the range of 95-99% for genotypes 1, 2, 3, 4, 5 and 6. In decompensated cirrhosis, sofosbuvir/velpatasvir plus ribavirin for 12 weeks achieved overall SVR of 94%. |
| Safety | • Most common adverse reactions of sofosbuvir/velpatasvir (≥10%) were fatigue and headache. In patients with decompensated cirrhosis that received sofosbuvir/velpatasvir with ribavirin, the most common adverse reactions (≥10%) were fatigue, anemia, nausea, headache, insomnia, and diarrhea. |
| Potential Impact | • Sofosbuvir/velpatasvir is pan-genotypic approved in adult patients with chronic HCV Genotype 1, 2, 3, 4, 5 or 6 infection; its greatest impact over existing regimens will be for Genotypes 2 and 3. It is available as a fixed-dose combination of sofosbuvir/velpatasvir that is administered once-daily for 12 weeks in patients without cirrhosis or with compensated cirrhosis (Child-Pugh A) or in combination with ribavirin in patients with decompensated cirrhosis. |

## Background

**Purpose for review**

The purpose of the review is to evaluate the efficacy and safety of the fixed-dose combination of sofosbuvir/velpatasvir.

**Other therapeutic options**

| Formulary Alternatives for interferon free HCV regimens | Other Considerations |
|---|---|
| Daclatasvir plus sofosbuvir | FDA approved for HCV GT1 and 3 including post-transplant patients<br>2 pills once a day (i.e., not a fixed-dose combination product) |
| Elbasvir/grazoprevir | FDA approved for HCV GT1 and 4 |

| | |
|---|---|
| | For HCV Genotype 1a patients, the prescribing information recommends baseline testing for the presence of virus with NS5A resistance-associated polymorphisms (RAPs) to guide the regimen. Because of lower SVRs in GT1a patients with baseline NS5A polymorphisms, these patients should receive elbasvir/grazoprevir plus ribavirin for 16 weeks.<br><br>No dosage adjustment is required in patients receiving elbasvir/grazoprevir with mild, moderate or severe renal impairment including hemodialysis. |
| Ledipasvir/sofosbuvir (Harvoni) | Drug interactions with PPIs and H2 blockers<br><br>FDA approved for HCV GT1, 4, 5 and 6<br><br>The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30mL/min/1.73m$^2$. |
| Ombitasvir, paritaprevir/ritonavir plus dasabuvir (Viekira Pak) for HCV GT1 or Ombitasvir, paritaprevir/ritonavir (Technivie) for HCV GT4 | Viekira Pak and Technivie contains ritonavir; thus, potential for significant drug-drug interactions including antiretrovirals<br><br>Technivie only FDA approved for HCV GT4 patients without cirrhosis |
| Sofosbuvir plus simeprevir | 2 pills once a day (i.e., not a fixed-dose combination product)<br><br>Simeprevir plus sofosbuvir should not be used in patients that experienced previous virologic failure with a NS3-4A protease inhibitor containing regimen (e.g., boceprevir or telaprevir). |
| Sofosbuvir plus ribavirin | FDA approved for HCV GT2 and GT3 |

## Efficacy (FDA Approved Indications)[1-4]

**Literature Search Summary**
A literature search was performed on PubMed/Medline (1966 to July 2016) using the search term velpatasvir. The search was limited to studies performed in humans and published in the English language. The pivotal phase 3 clinical trials published in peer-reviewed journals were included.

**Review of Efficacy**
The FDA approval of sofosbuvir/velpatasvir was based on four pivotal Phase 3 randomized, open-label trials (ASTRAL-1, ASTRAL-2, ASTRAL-3 and ASTRAL-4).[1-4] The ASTRAL 1-3 trials evaluated the use of sofosbuvir/velpatasvir in HCV genotype 1-6 patients with compensated liver disease with and without cirrhosis for a treatment duration of 12 weeks. ASTRAL-4 randomized patients with Child-Pugh B decompensated cirrhosis to receive (1:1:1) SOF/VEL for 12 weeks, SOF/VEL+RBV for 12 weeks or SOF/VEL for 24 weeks. Primary efficacy endpoint was sustained viral response (SVR)

defined as HCV RNA less than 15 IU/mL at 12 weeks post-treatment. Refer to Table 1 for SVRs according to data provided in the prescribing information.[1] Refer to Table 2 for SVRs published in the literature for the ASTRAL studies.[2-4]

**Table 1. Summary of Phase 3 Clinical Trials supporting FDA indications[a]**

| Study | Population | Regimen | SVR12 |
|---|---|---|---|
| ASTRAL-1 | Treatment-naïve and experienced HCV Genotype 1,2,4,5 and 6 patients with or without cirrhosis | SOF/VEL for 12 wks<br>Placebo | 618/624 (99%)<br>Not reported |
| ASTRAL-2 | Treatment-naïve and experienced HCV Genotype 2 patients with or without cirrhosis | SOF/VEL for 12 wks<br>SOF + RBV for 12 wks | 133/134 (99%)<br>124/132 (94%) |
| ASTRAL-3 | Treatment-naïve and experienced HCV Genotype 3 patients with or without cirrhosis | SOF/VEL for 12 wks<br>SOF + RBV for 24 wks | 264/277 (95%)<br>221/275 (80%) |
| ASTRAL-4 | Treatment-naïve and experienced HCV Genotype 1,2,3,4,5 and 6 patients with decompensated Child-Pugh cirrhosis | SOF/VEL for 12 wks<br>SOF/VEL+RBV for 12 wks<br>SOF/VEL for 24 wks | Not reported<br>82/87 (94%)<br>Not reported |

[a]Data reported according to prescribing information[1]; p-values nor 95% CI were not reported; SOF/VEL: sofosbuvir/velpatasvir; RBV: ribavirin

**Table 2. Summary of Phase 3 Clinical Trials reported in published literature[2-4]**

| Study | Population | Regimens | GT SVR12 | 95% CI |
|---|---|---|---|---|
| ASTRAL-1 | Treatment-naïve and experienced HCV Genotype 1,2,4,5 and 6 patients with or without cirrhosis | SOF/VEL for 12 wks | 1a: 206/210 (98%)<br>1b: 117/118 (99%)<br>2: 104/104 (100%)<br>4: 116/116 (100%)<br>5: 34/35 (97%)<br>6: 41/41 (100%) | (95 to >99)<br>(95 to 100)<br>(97 to 100)<br>(97 to 100)<br>(85 to >99)<br>(91 to 100) |
| ASTRAL-2 | Treatment-naïve and experienced HCV Genotype 2 patients with or without cirrhosis | SOF/VEL for 12 wks<br>SOF plus RBV for 12 wks | 133/134 (99%)<br>124/132 (94%) | (96 to 100)<br>(88 to 97) |
| ASTRAL-3 | Treatment-naïve and experienced HCV Genotype 3 patients with or without cirrhosis | SOF/VEL for 12 wks<br>SOF plus RBV for 24 wks | 264/277 (95%)<br>221/275 (80%) | (92 to 98)<br>(75 to 85) |
| ASTRAL-4 | Treatment-naïve and experienced HCV Genotype 1,2,3,4,5 and 6 patients with decompensated Child-Pugh cirrhosis | SOF/VEL for 12 wks<br>SOF/VEL+RBV for 12 wks<br>SOF/VEL for 24 wks | All genotypes*<br>75/90 (83%)<br>82/87 (94%)<br>77/90 (86%) | <br>(74-90)<br>(87-98)<br>(77-92) |

*Breakdown by genotype can be found in ASTRAL-4 review below. Overall Quality of Evidence: High (Refer to Appendix A; note all three pivotal clinical trials sponsored by Gilead); GT, genotype; SOF/VEL, sofosbuvir/velpatasvir; SOF, sofosbuvir; RBV, ribavirin

**ASTRAL-1: Treatment-naïve and experienced HCV Genotype 1,2,4,5 and 6 patients with or without compensated cirrhosis[2]**

- Double-blind, placebo-controlled, randomization in 5:1 ratio to receive sofosbuvir/velpatasvir or placebo for 12 weeks.
- Demographics of SOF/VEL group included median age 54 years old (range: 18 to 82); 60% male; 79% white, 8% black, 10% Asian; 46% from North America; 74% baseline HCV RNA ≥ 800,000 IU/mL; 34% genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5 and 7% genotype 6; 69% non-C/C IL28B alleles (CT or TT); 19% cirrhotic ; 32% treatment-experienced 28% of which had received prior protease inhibitor/peginterferon/ribavirin therapy.
- Baseline NS5B resistance was present in 9% of patients; all of these patients achieved SVR
- Two patients experienced virologic failure and both had NS5A resistance at baseline and at the time of relapse. The GT1a patient had the Q30R variant at baseline but the Y93N variant at the time of relapse. The GT1b patient had Q30L/R and L31M at baseline and the Q30R, L31M, and Y93H at the time of relapse.

| | SVR12 |
|---|---|
| | Sofosbuvir/velpatasvir for 12 weeks |
| Genotype | |

| | |
|---|---|
| Genotype 1a | 206/210 (98%) |
| Genotype 1b | 117/118 (99%) |
| Genotype 2 | 104/104 (100%) |
| Genotype 4 | 116/116 (100%) |
| Genotype 5 | 34/35 (97%) |
| Genotype 6 | 41/41 (100%) |
| Cirrhosis (all genotypes) | 120/121 (99%) |
| Treatment-experienced (all genotypes) | 200/201 (99.5%) |
| Virologic failure post-treatment | 2 (<1%) |

P-values not provided in prescribing information

**ASTRAL-2 and ASTRAL-3: Treatment-naïve and experienced HCV Genotype 2 and 3 patients with or without compensated cirrhosis[3]**

*Astral-2*

- Randomization in 1:1 ratio to receive SOF/VEL or SOF + RBV for 12 weeks
- Demographics included mean age 57 years old (range: 26 to 81); 64% male; 93% white, 4% black; mean BMI 28; 83% baseline HCV RNA ≥ 800,000 IU/mL; 59% non-C/C IL28B alleles (CT or TT); 14% cirrhotics and 14% treatment-experienced.
- SOF/VEL SVR rate was superior to that of SOF+RBV, with an absolute difference of 5.2% (95%CI 0.2-10.3, p=0.02)
- SVR rates by patient subgroups were not provided

| | **SVR at 12 weeks** | |
|---|---|---|
| | **SOF/VEL 12 week regimen** | **SOF + RBV 12 week regimen** |
| Overall | 133/134 (99%) | 124/132 (94%) |
| Virologic failure | 0 | 6/132(5%) |

*Astral-3*

- Randomization in 1:1 ratio to receive SOF/VEL for 12 weeks or SOF + RBV for 24 weeks
- Demographics of the SOF/VEL group included mean age 49 years old (range: 21 to 76); 61% male; 90% white, 1% Black, 8% Asian; mean BMI 26; 69% baseline HCV RNA ≥ 800,000 IU/mL; 62% non-C/C IL28B alleles (CT or TT); 29% cirrhotic and 26% treatment-experienced.
- The SVR rate with SOF/VEL for 12 weeks was superior to that of SOF+RBV for 24 weeks, with an absolute difference of 14.8% (95%CI 9.6-20.0, p<0.001)
- NS5A RAVs were present in 16% of patients at baseline and of these, 88% achieved SVR; 84% of patients with the Y93H variant at baseline achieved SVR. In those patients without baseline NS5A resistance, the SVR rate was 97% (225/231)
- Ten patients had baseline NS5B resistance, all of whom achieved SVR

| | **SOF/VEL 12 week regimen** | **SOF + RBV 24 week regimen** |
|---|---|---|
| Overall | 264/277 (95%) | 221/275 (80%) |
| Cirrhosis | | |
| With | (91%) | (66%) |
| Without | (97%) | (87%) |
| Treatment-experienced | | |
| Yes | (90%) | (63%) |
| No | (97%) | (86%) |
| Treatment-naive **with** cirrhosis | 40/43 (93%) | 33/45 (73%) |
| Treatment-naive **without** cirrhosis | 160/163 (98%) | 141/156 (90%) |
| Treatment-experienced **with** cirrhosis | 33/37 (89%) | 22/38 (58%) |
| Treatment-experienced **without** cirrhosis | 31/34 (91%) | 22/31 (71%) |
| Virologic failure | 11/276 (4%) | 38/272 (14%) |

**ASTRAL-4 Treatment-naïve and experienced patients with HCV Genotype 1 through 6 and decompensated (Child-Pugh-Turcotte class B) cirrhosis[4]**

- Randomization in 1:1:1 ratio to receive SOF/VEL for 12 weeks, SOF/VEL plus RBV for 12 weeks, or SOF/VEL for 24 weeks
- Demographics of the cohort included mean age 58 years old (range: 42 to 73); 57-66% male; 88-91% white, 6-7% black; 50-66% baseline HCV RNA ≥ 800,000 IU/mL; 60% genotype 1a, 18% genotype 1b, 4% genotype 2, 15% genotype 3, 3% genotype 4 and <1% genotype 6; 55% treatment-experienced of which 16-26% received prior protease inhibitor regimens; median baseline CPT score was 8 (range 5-10), median baseline MELD was 10 (range 6-24).
- Post-hoc analysis did not detect any significant differences between the three groups
- Of patients with CPT and MELD scores available 12 weeks post-treatment, 47% had an improvement in CPT score over baseline (117/250) and 51% had improved MELD score (114/223)
- 72/255 patients had baseline NS5A RAVs and 89% (64/72) achieved SVR compared to a 92% SVR in those without baseline NS5A RAVs.
- 100% of GT1 patients with NS5A baseline RAVs receiving SOF/VEL+RBV achieved SVR.
- 80% of GT1 patients receiving SOF/VEL for 12 weeks and 90% of patients receiving SOF/VEL for 24 weeks with baseline NS5A RAVs achieved SVR, respectively.
- Impact of baseline RAVs in GT3 could not be assessed because of small numbers of patients with baseline RAVs
- 3% of patients had NS5B RAVs at baseline (8/251) and all achieved an SVR

| | SVR | | |
|---|---|---|---|
| **Subgroups** | **SOF/VEL 12 week regimen** | **SOF/VEL + RBV 12 week regimen** | **SOF/VEL 24 week regimen** |
| Overall | 75/90 (83%) | 82/87 (94%) | 77/90 (86%) |
| Genotype 1a | 44/50 (88%) | 51/54 (94%) | 51/55 (93%) |
| Genotype 1b | 16/18 (89%) | 14/14 (100%) | 14/16 (88%) |
| Genotype 2 | 4/4 (100%) | 4/4 (100%) | 3/4 (75%) |
| Genotype 3 | 7/14 (50%) | 11/13 (85%) | 6/12 (50%) |
| Genotype 4 | 4/4 (100%) | 2/2 (100%) | 2/2 (100%) |
| Genotype 6 | 0 | 0 | 1/1 |
| Virologic Failure | | | |
| Genotype 1a | 3/50 (6%) | 1/54 (2%) | 2/55 (4%) |
| Genotype 1b | 2/18 (11%) | 0 | 1/16 (6%) |
| Genotype 3 | 6/14 (43%) | 2/13 (15%) | 5/12 (42%) |

**Summary of efficacy**

- SOF/VEL achieved SVRs in the range of 97%-100% in treatment-naïve and experienced patients with HCV genotype 1,2,4,5 and 6 with or without compensated cirrhosis. SVRs in genotype 3 patients ranged from 89%-98% in treatment-naïve and experienced patients with or without compensated cirrhosis. In HCV genotype 1,2,3,4 and 6 patients with decompensated Childs-Pugh B cirrhosis receiving SOF/VEL±RBV for 12 or 24 weeks, SVRs ranged from 83%-94% overall, however, variation in SVR occurred among genotypes, the presence of baseline NS5A RAVS, and regimen.

## Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

- None identified

## Safety (for more detailed information refer to the product package insert)[1]

| | Comments |
|---|---|
| **Boxed Warning** | • None |
| **Contraindications** | • Use of sofosbuvir/velpatasvir in combination with ribavirin is contraindicated in patients for whom ribavirin is contraindicated |
| **Warnings/Precautions** | • Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone and sofosbuvir/velpatasvir is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended. |
| **Safety Considerations** | |

The safety assessment of sofosbuvir/velpatasvir was based on pooled data from 1035 patients in three Phase 3 clinical trials of subjects with genotype 1, 2, 3, 4, 5, or 6 chronic hepatitis C with compensated liver disease (with and without cirrhosis) for duration of 12 weeks while safety in decompensated cirrhosis was based upon one Phase 3 trial of 87 patients with HCV genotype 1, 2, 3, 4 or 6.

**Adverse Reactions**

| | |
|---|---|
| Common adverse reactions | Most common adverse reactions of sofosbuvir/velpatasvir (≥10%) were fatigue and headache. In patients with decompensated cirrhosis that received sofosbuvir/velpatasvir and ribavirin, the most common adverse reactions (≥10%) were fatigue, anemia, nausea, headache, insomnia, and diarrhea. |
| Death/Serious adverse reactions | Deaths/serious adverse reactions were not addressed in the prescribing information. |
| Discontinuations due to adverse reactions | In patients with compensated liver disease, 0.2% discontinued due to adverse events while 5% of decompensated patients discontinued due to adverse events. |
| Laboratory Abnormalities | **Lipase Elevations:** In ASTRAL-1, asymptomatic lipase elevations of greater than 3xULN were observed in 3% of subjects treated sofosbuvir/velpatasvir for 12 weeks compared to 1% treated with placebo. In ASTRAL-2 and ASTRAL-3, asymptomatic lipase elevations of greater than 3xULN were observed in 3% compared to 1%, respectively. In ASTRAL-4, asymptomatic lipase elevations of greater than 3xULN were observed in 3% of subjects treated sofosbuvir/velpatasvir with ribavirin for 12 weeks.<br>**Creatine Kinase:** In ASTRAL-1, asymptomatic creatine kinase elevations of greater than or equal to 10xULN were observed in 1% of subjects treated sofosbuvir/velpatasvir for 12 weeks compared to 0% treated with placebo. In ASTRAL-2 and ASTRAL-3, asymptomatic creatine kinase elevations greater than or equal than 10xULN were observed in 2% compared to 1%, respectively. In ASTRAL-4, asymptomatic creatine elevations of greater than or equal than 10xULN were observed in 1% of subjects treated sofosbuvir/velpatasvir with ribavirin for 12 weeks. |

**Drug-Drug Interactions**[1]

- Consult the prescribing information prior to use of sofosbuvir/velpatasvir regimen for potential drug interactions.
    - Sofosbuvir and velpatasvir are substrates of drug transporter P-gp and breast cancer resistance protein (BCRP); drugs that are potent P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir and velpatasvir plasma concentrations.
    - Velpatasvir is an inhibitor of the drug transporter P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1; co-administration of sofosbuvir/velpatasvir with drugs that are substrates of these transporters may increase the exposure of such drugs.
- Sofosbuvir/velpatasvir should NOT be coadministrated with proton-pump inhibitors (unless medically necessary; more details below), rifampin, rifabutin, rifapentine, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, tipranavir/ritonavir, rosuvastatin (greater than 10mg/day), topotecan, efavirenz, or amiodarone.
- Other potentially significant drug interactions may include:
    - Sofosbuvir/velpatasvir may increase concentration of digoxin when co-administered; therapeutic monitoring of digoxin is recommended.
    - Sofosbuvir/velpatasvir may increase the concentration of tenofovir DF; monitor for tenofovir-associated adverse events.
    - Sofosbuvir/velpatasvir may increase HMG-CoA reductase inhibitors. Monitor for closely for adverse events such as myopathy and rhabdomyolysis. Rovustatin should not exceed a dose of 10mg/day.
- Drugs that increase gastric pH are expected to decrease absorption and blood concentration of velpatasvir
    - Separate antacids and sofosbuvir/velpatasvir administration by 4 hours.
    - H2-receptor antagonists may be administered simultaneously with or 12 hours apart from sofosbuvir/velpatasvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily

- Co-administration of omeprazole or other proton-pump inhibitors are not recommended with sofosbuvir/velpatasvir. If possible, consideration should be given to discontinuing the PPI during SOF/VEL treatment. If the PPI is deemed medically necessary, sofosbuvir/velpatasvir should be administered with food and taken 4 hours before omeprazole 20mg/day OR consider using daclatasvir+sofosbuvir±ribavirin as an alternative regimen.

## Risk Evaluation

| As of July 2016 | Comments |
|---|---|
| Sentinel event advisories | • None |
| Look-alike/sound-alike error potentials | • Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List): |

| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
|---|---|---|---|---|
| Sofosbuvir-Velpatasivir 400mg, 100mg tab | None | None | None | Sofosbuvir<br>Sofosbuvir-Ledipasvir<br>Sacubitril-Valsartan |
| Epclusa | None | None | None | Epanova<br>Iclusig |

## Other Considerations

- None

## Dosing and Administration[1]

Sofosbuvir/velpatasvir is a fixed-dose combination:
One tablet (400mg of sofosbuvir and 100mg velpatasvir) taken orally once daily with or without food.

When sofosbuvir-containing regimen is used in combination with ribavirin therapy, ribavirin should be administered in 2 divided doses with food [<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day unless patient has decompensated cirrhosis (CTP B or C) in which case ribavirin 600 mg/day is recommended].

| Population includes patients with HCV monoinfection, HCV/HIV-1 co-infection, or hepatocellular carcinoma (HCC) | Dosage Regimens | Total treatment duration |
|---|---|---|
| **HCV Genotype 1, 2, 3, 4, 5 or 6**<br>Without cirrhosis or with compensated cirrhosis (CTP A) | Sofosbuvir/velpatasvir | 12 weeks |
| Decompensated cirrhosis (CTP B or C) | Sofosbuvir/velpatasvir plus ribavirin[a] | 12 weeks |

[a]Initiate ribavirin at 600mg/day and titrate up as tolerated based upon expert opinion; FDA labeling recommends weight-based ribavirin dosage regimen

## Special Populations (Adults)[1]

| | Comments |
|---|---|
| **Elderly** | • Clinical trials included 156 subjects aged 65 and over. No overall differences in safety or effectiveness were observed. |
| **Pregnancy** | • If sofosbuvir/velpatasvir is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant.<br>• If sofosbuvir/velpatasvir is administered without ribavirin, no adequate human data are available to establish whether or not it |

| | |
|---|---|
| | poses a risk to pregnancy outcomes. |
| **Lactation** | • It is not known whether sofosbuvir/velpatasvir and its metabolites are present in human breast milk. According to PI, the developmental and health benefits of breastfeeding should be considered along with mother's clinical need and potential adverse effects on child from drugs or underlying maternal condition. If co-administered with ribavirin, refer to ribavirin prescribing information. |
| **Renal Impairment** | • No dosage adjustment is necessary for patients receiving sofosbuvir/velpatasvir with mild or moderate renal impairment; sofosbuvir/velpatasvir was not studied in patients with severe renal impairment (<30mL/min), end-stage renal disease or on hemodialysis. The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min. If co-administered with ribavirin, refer to ribavirin prescribing information for renal dose adjustment. |
| **Hepatic Impairment** | • No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment. |
| **Pharmacogenetics/genomics** | • No data identified in prescribing information. |

## Projected Place in Therapy

Sofosbuvir/velpatasvir is pan-genotypic approved in adult patients with chronic HCV Genotype 1, 2, 3, 4, 5 or 6 infection; its greatest impact over existing regimens will be for Genotypes 2 and 3. It is available as a fixed-dose combination of sofosbuvir/velpatasvir that is administered once-daily for 12 weeks in patients without cirrhosis or with compensated cirrhosis (Child-Pugh A) or in combination with ribavirin in patients with decompensated cirrhosis.

## References


1. Epclusa [package insert]. Gilead Sciences, Inc., Foster City, CA; June 2016.
2. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med. 2015 Dec 31;373(27):2599-607. doi: 10.1056/NEJMoa1512610. Epub 2015 Nov 16.
3. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med. 2015 Dec 31;373(27):2608-17. doi: 10.1056/NEJMoa1512612. Epub 2015 Nov 17.
4. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med. 2015 Dec 31;373(27):2618-28. doi: 10.1056/NEJMoa1512614. Epub 2015 Nov 16.



**Prepared: Melinda Neuhauser, PharmD, MPH and Pam Belperio, PharmD, July 2016**
**Contact person: Melinda Neuhauser, PharmD, MPH, PBM Services**

**Appendix A: GRADEing the Evidence**

Designations of Quality

| Quality of evidence designation | Description |
|---|---|
| High | Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects). |
| Moderate | Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence. |
| Low | Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. |

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.