Medicaid P & T Committee
EPCLUSA® (sofosbuvir and velpatasvir)
Gilead Sciences, Inc

EPCLUSA® is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor. Each tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir, and each 200 mg/50 mg tablet contains 200 mg of sofosbuvir and 50 mg of velpatasvir. EPCLUSA is a protease inhibitor (PI)-free all oral complete daily regimen in a single tablet, also known as a single tablet regimen (STR).[1] EPCLUSA is indicated for the treatment of adult and pediatric patients 6 years of age and older or weighing at least 17 kg with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis and in combination with ribavirin (RBV) in patients with decompensated cirrhosis (DCC). EPCLUSA is the first pangenotypic, panfibrotic, PI-free, single duration STR (one tablet daily) HCV regimen that provides consistent, simple dosing (12 weeks) for all patients, regardless of treatment experience or presence of compensated cirrhosis.

**Dosing Regimen:** The recommended dose of EPCLUSA in adults is one tablet (400 mg sofosbuvir and 100 mg velpatasvir) taken once daily, with or without food, with no requirement for baseline NS5A resistance-associated variant (RAV) testing. No dosage adjustments are recommended in patients with any degree of renal impairment, including patients requiring dialysis.[1]
The recommended dose of EPCLUSA in pediatric patients 6 years of age and older and weighing at least 30 kg is one tablet (400 mg sofosbuvir and 100 mg velpatasvir) or two 200 mg sofosbuvir and 50 mg velpatasvir (equivalent to 400 mg sofosbuvir and 100 mg velpatasvir) tablets taken once daily. For those pediatric patients weighing 17 kg to less than 30 kg, the recommended dose is one 200 mg sofosbuvir and 50 mg velpatasvir tablet taken once daily.[1]

**Table 1. Recommended Treatment Regimen and Duration for EPCLUSA in Patients 6 Years of Age and Older or Weighing at Least 17 kg with GT 1, 2, 3, 4, 5, or 6[1]**

| Patient Population | Treatment Regimen and Duration |
|---|---|
| Treatment-naïve and treatment-experienced[a], without cirrhosis and with compensated cirrhosis (Child-Pugh A) | EPCLUSA 12 weeks |
| Treatment-naïve and treatment-experienced with decompensated cirrhosis (Child-Pugh B and C) | EPCLUSA + RBV[b,c] 12 weeks |

[a] In clinical trials, regimens contained peginterferon alfa/ribavirin with or without an HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir).
[b] When administered with EPCLUSA, the recommended dosage of ribavirin is based on weight (administered with food): 1000 mg per day for adults less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily. The starting dosage and on-treatment dosage of ribavirin can be decreased based on hemoglobin and creatinine clearance. For ribavirin dosage modifications, refer to the ribavirin prescribing information.
[c] For pediatric patients, the daily dose of ribavirin is weight-based and is administered orally in two divided doses with food. See the EPCLUSA prescribing information for details.

**Potent Efficacy with High SVR Rates:** Table 2 presents the SVR results from each of the key clinical studies with EPCLUSA.[1-6]

**Table 2. SVR12 Results for Key Studies of EPCLUSA with or without Ribavirin [1-6,11,12,13]**

| Patient Population | Treatment Regimen and Duration | SVR12 | Relapse Rate[c] | Clinical Trial Source |
|---|---|---|---|---|
| GT1a | EPCLUSA 12 weeks | 98% (206/210) | <1% (1/209) | ASTRAL-1 |
| GT1b | | 99% (117/118) | 1% (1/118) | ASTRAL-1 |
| GT2 | | 100% (104/104) | 0% | ASTRAL-1 |
| | | 99% (133/134) | 0%[a] | ASTRAL-2 |
| GT3 | | 95% (264/277) | 4% (11/276) | ASTRAL-3 |
| GT4 | | 100% (116/116) | 0% | ASTRAL-1 |
| GT5 | | 97% (34/35) | 0%[b] | ASTRAL-1 |
| GT6 | | 100% (41/41) | 0% | ASTRAL-1 |
| HIV/HCV Co-infected GT1, 2, 3, 4 | | 95% (101/106) | 2% (2/103) | ASTRAL-5 |
| Decompensated Cirrhotics | EPCLUSA + RBV 12 weeks | 94% | 3% (3/87) | ASTRAL-4 |
| Post-Liver Transplant | EPCLUSA 12 weeks | 96% | 3% (2/79) | Trial 2104 |
| Severe Renal Impairment Requiring Dialysis | EPCLUSA 12 weeks | 95% (56/59) | 2% (1/56) | Trial 4062 |
| Pediatrics 6 years of age and older | EPCLUSA 12 weeks | 92% (67/73)[d]; 95% (97/102)[e] | <1% (1/102)[e] | Trial 1143 |

[a] 1 patient lost to follow-up
[b] 1 patient died; 55-year-old white male died in sleep 8 days after completing treatment; death assessed as unrelated to study drug by investigator
[c] The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
[d] 6-11 year old
[e] 12-17 year old

**Low Discontinuation Rates**
When EPCLUSA was administered to GT 1 – 6 patients without cirrhosis and with compensated cirrhosis, discontinuation due to adverse events occurred in 0.2% of patients. When EPCLUSA and ribavirin was administered to GT 1,2,3,4 or 6 decompensated patients, discontinuation due to adverse events occurred in 5% of patients.[1] Adverse reactions observed in pediatric patients 6 years of age and older were consistent with those observed in clinical trials of EPCLUSA in adults.[1] Adverse reactions observed in adult liver transplant recipients were consistent with the known safety profile of EPCLUSA.[1]

**Real World SVR Rates**
Real world SVR rates for EPCLUSA across GT 1-6, in the Target Registry, TRIO Registry, and Italian Real World Registry, are similar to those in clinical trials[7-10]

**BOXED WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV**
**Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with EPCLUSA. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.**

**Contraindications**
If EPCLUSA is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information.[1]

**Warnings and Precautions**
- **Risk of Serious Symptomatic Bradycardia When Coadministered with Amiodarone:** Amiodarone is not recommended for use with EPCLUSA due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. In patients without alternative, viable treatment options, in-patient cardiac monitoring is recommended for the first 48 hours after which outpatient monitoring of heart rate should occur on a daily basis through at least the first 2 weeks. Patients should be counseled about the risk of symptomatic bradycardia.
- **Risk of Reduced Therapeutic Effect of EPCLUSA Due to P-gp Inducers and/or Moderate to Strong Inducers of CYP:** Rifampin, St. John's wort and carbamazepine are not recommended for use with EPCLUSA as they may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.[1]

**Adverse Reactions**
The most common adverse reactions (≥10%, all grades) with EPCLUSA were headache and fatigue; and when used with RBV in patients with decompensated cirrhosis were fatigue, anemia, nausea, headache, insomnia, and diarrhea.[1]

**Drug Interactions**
- In addition to amiodarone, rifampin, St. John's wort, and carbamazepine, coadministration of EPCLUSA is also not recommended with phenobarbital, phenytoin, rifabutin, rifapentine, efavirenz and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of velpatasvir and/or sofosbuvir, reducing the therapeutic effect of EPCLUSA.[1]
- Coadministration is also not recommended with topotecan due to increased concentrations of topotecan.[1]

**Additional Drug Interactions**
The absorption of velpatasvir is partially dependent on acidic conditions in the stomach. It is recommended to separate antacids and EPCLUSA administration by 4 hours. EPCLUSA may be administered simultaneously or 12 hours apart with an H2-receptor antagonist at a dose that does not exceed the equivalent of famotidine 40 mg twice daily. Coadministration of EPCLUSA is not recommended with omeprazole or other proton-pump inhibitors due to expected decreases in the concentration of velpatasvir. If omeprazole is considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20mg.[1]

**Drugs without Clinically Significant Interactions with EPCLUSA**
Based on drug interaction studies conducted with the components of EPCLUSA (velpatasvir or sofosbuvir) or EPCLUSA, no clinically significant drug interactions have been observed with the following drugs:[1]
- EPCLUSA: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir, or rilpivirine
- Sofosbuvir: ethinyl estradiol/norgestimate, methadone, or tacrolimus
- Velpatasvir: ethinyl estradiol/norgestimate, ketoconazole, or pravastatin

**Summary**
EPCLUSA, a pangenotypic, panfibrotic, PI-free regimen, resulted in high SVR rates (94-100%) in patients with chronic HCV GT 1 – 6 without cirrhosis or with compensated cirrhosis and in combination with RBV in patients with decompensated cirrhosis. High SVR12 rates were achieved with EPCLUSA for 12 weeks by subjects in the ASTRAL 1, 2 and 3 trials irrespective of number of negative predictive factors evaluated (presence of NS5A RAVs, cirrhosis, baseline HCV RNA ≥ 800,000 IU/mL, and prior treatment) and EPCLUSA does not require baseline RAV testing. Real world data SVR rates for EPCLUSA are similar to those in clinical trials. EPCLUSA has limited drug-drug interactions and was well-tolerated with low rates of discontinuations due to adverse events (0.2% in patients without

cirrhosis and with compensated cirrhosis; 5% when used with RBV in patients with decompensated cirrhosis). EPCLUSA provides consistent cure rates across genotypes and patients in both clinical trials and real world studies. No dosage requirement is recommended in patients with any degree of renal impairment, including patients requiring dialysis. Patients as young as 6 years of old or weighing at least 17 kg can now have this effective HCV treatment option.

**References**


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