HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPCLUSA safely and effectively. See full prescribing information for EPCLUSA.

EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

----------RECENT MAJOR CHANGES----------

Boxed Warning	02/2017
Dosage and Administration (2.1)	02/2017
Warnings and Precautions (5.1)	02/2017

----------INDICATIONS AND USAGE----------

EPCLUSA is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection (1):

- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis for use in combination with ribavirin

----------DOSAGE AND ADMINISTRATION----------

- Testing Prior to the Initiation of Therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Recommended dosage: One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily with or without food (2.2)
- See recommended treatment regimen and duration in patients with genotypes 1, 2, 3, 4, 5, or 6 HCV in table below: (2.2)

Patient Population	Recommended Treatment Regimen
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	EPCLUSA for 12 weeks
Patients with decompensated cirrhosis (Child-Pugh B and C)	EPCLUSA + ribavirin for 12 weeks

- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 400 mg sofosbuvir and 100 mg velpatasvir (3)

----------CONTRAINDICATIONS----------

EPCLUSA and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Hepatitis B Virus Reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)
- 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 with EPCLUSA is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended. (5.2, 7.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with EPCLUSA for 12 weeks are headache and fatigue. (6.1)
- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with EPCLUSA and ribavirin for 12 weeks in patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- P-gp inducers and/or moderate to potent CYP inducers (e.g., rifampin, St. John's wort, carbamazepine): May decrease concentrations of sofosbuvir and/or velpatasvir. Use of EPCLUSA with P-gp inducers and/or moderate to potent CYP inducers is not recommended (5.3, 7)
- Consult the full prescribing information prior to use for potential drug interactions (5.2, 5.3, 7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2017

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FULL PRESCRIBING INFORMATION

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 *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

EPCLUSA is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection *[see Dosage and Administration (2) and Clinical Studies (14)]*:

- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis for use in combination with ribavirin

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to the Initiation of Therapy

Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with EPCLUSA *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

The recommended dosage of EPCLUSA is one tablet taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]*. One tablet of EPCLUSA contains 400 mg of sofosbuvir and 100 mg of velpatasvir. Table 1 shows the recommended treatment regimen and duration based on patient population.

Table 1 Recommended Treatment Regimen in Patients with Genotype 1, 2, 3, 4, 5, or 6 HCV

Patient Population	Treatment Regimen and Duration
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	EPCLUSA 12 weeks
Patients with decompensated cirrhosis (Child-Pugh B or C)	EPCLUSA + ribavirin[a] 12 weeks

a. When administered with EPCLUSA, the recommended dosage of ribavirin is based on weight (administered with food): 1000 mg per day for patients 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.

2.3 No Dosage Recommendations in Severe Renal Impairment and End Stage Renal Disease

No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73 m^2) or with end stage renal disease (ESRD), due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Each EPCLUSA tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir. The tablets are pink, diamond-shaped, film-coated, and debossed with “GSI” on one side and “7916” on the other side.

4 CONTRAINDICATIONS

EPCLUSA and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressants or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increases in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with EPCLUSA. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with EPCLUSA and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

5.2 Serious Symptomatic Bradycardia When Sofosbuvir Is Coadministered with Amiodarone and Another HCV Direct-Acting Antiviral

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with daclatasvir or simeprevir. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (HARVONI (ledipasvir/sofosbuvir)). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with EPCLUSA is not recommended. For patients taking amiodarone who have no other alternative viable treatment options and who will be coadministered EPCLUSA:

- Counsel patients about the risk of symptomatic bradycardia.
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking EPCLUSA who need to start amiodarone therapy due to no other alternative viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting EPCLUSA should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems *[see Adverse Reactions (6.2) and Drug Interactions (7.3)]*.

5.3 Risk of Reduced Therapeutic Effect Due to Concomitant Use of EPCLUSA with Inducers of P-gp and/or Moderate to Potent Inducers of CYP

Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to potentially reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended *[see Drug Interactions (7.3)]*.

5.4 Risks Associated with Ribavirin and EPCLUSA Combination Treatment

If EPCLUSA is administered with ribavirin, the warnings and precautions for ribavirin apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin *[see Dosage and Administration (2.2)].*

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