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

----------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----------
- Recommended dosage: One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily with or without food (2.1)
- See recommended treatment regimen and duration in patients with genotypes 1, 2, 3, 4, 5, or 6 HCV in table below: (2.1)

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 (2.2)

----------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----------
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. (5.1, 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 (5.2, 7)
- Consult the full prescribing information prior to use for potential drug interactions (5.1, 5.2, 7)

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

Revised: 06/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 (2.1) 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 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.

2.2 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 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)]*.

5.2 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)]*.

5.3 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 (2.1)].*

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Serious Symptomatic Bradycardia When Sofosbuvir Is Coadministered with Amiodarone and Another HCV Direct Acting Antiviral *[see Warnings and Precautions (5.1)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

If EPCLUSA is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions.

Adverse Reactions in Subjects without Cirrhosis or with Compensated Cirrhosis

The adverse reactions data for EPCLUSA in patients without cirrhosis or with compensated cirrhosis were derived from three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which evaluated a total of 1035 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV, without cirrhosis or with compensated cirrhosis, who received EPCLUSA for 12 weeks. EPCLUSA was studied in placebo- and active-controlled trials [*see Clinical Studies (14.2)*].

The proportion of subjects who permanently discontinued treatment due to adverse events was 0.2% for subjects who received EPCLUSA for 12 weeks.

The most common adverse reactions (adverse events assessed as causally related by the investigator and at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks.

Adverse reactions, all grades, observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with EPCLUSA in ASTRAL-1 include headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Of subjects receiving EPCLUSA who experienced these adverse reactions, 79% had an adverse reaction of mild severity (Grade 1). With the exception of asthenia, each of these adverse reactions occurred at a similar frequency or more frequently in subjects treated with placebo compared to subjects treated with EPCLUSA (asthenia: 3% versus 5% for the placebo and EPCLUSA groups, respectively).

The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Irritability was also observed in greater than or equal to 5% of subjects treated with EPCLUSA in ASTRAL-3.

Adverse Reactions in Subjects with Decompensated Cirrhosis

The safety assessment of EPCLUSA in subjects infected with genotype 1, 2, 3, 4 or 6 HCV with decompensated cirrhosis was based on one Phase 3 trial (ASTRAL-4) including 87 subjects who received EPCLUSA with ribavirin for 12 weeks. All 87 subjects had Child-Pugh B cirrhosis at screening. On the first day of treatment with EPCLUSA with ribavirin, 6 subjects and 4 subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively *[see Clinical Studies (14.3)]*.

The most common adverse reactions (adverse events assessed as causally related by the investigator, all grades with frequency of 10% or greater) in the 87 subjects who received EPCLUSA with ribavirin for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%). Of subjects who experienced these adverse reactions, 98% had adverse reactions of mild to moderate in severity.

A total of 4 (5%) subjects permanently discontinued EPCLUSA with ribavirin due to an adverse event; there was no adverse event leading to discontinuation that occurred in more than 1 subject.

Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 23% and 7% of subjects treated with EPCLUSA with ribavirin for 12 weeks, respectively. Ribavirin was permanently discontinued in 17% of subjects treated with EPCLUSA with ribavirin for 12 weeks, due to adverse reactions.

Less Common Adverse Reactions Reported in Clinical Trials

The following adverse reactions occurred in less than 5% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks and are included because of a potential causal relationship.

Rash: In the ASTRAL-1 study, rash occurred in 2% of subjects treated with EPCLUSA and in 1% of subjects treated with placebo. No serious adverse reactions of rash occurred and all rashes were mild or moderate in severity.

Depression: In the ASTRAL-1 study, depressed mood occurred in 1% of subjects treated with EPCLUSA and was not reported by any subject taking placebo. No serious adverse reactions of depressed mood occurred and all events were mild or moderate in severity.

The following adverse reactions occurred in less than 10% of subjects with decompensated cirrhosis (ASTRAL-4) treated with EPCLUSA with ribavirin for 12 weeks and are included because of a potential causal relationship.

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