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

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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.

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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)].*

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 (5.2)].*

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.

<u>Adverse Reactions in Subjects without Cirrhosis or with Compensated Cirrhosis</u>

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.

<u>Adverse Reactions in Subjects with Decompensated Cirrhosis</u>

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

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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 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.

<u>Less Common Adverse Reactions Reported in Clinical Trials</u>

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.

Rash: Rash occurred in 5% of subjects treated with EPCLUSA with ribavirin. No serious adverse reactions of rash occurred and all rashes were mild or moderate in severity.

<u>Laboratory Abnormalities</u>

Lipase Elevations: In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 3% and 1% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively; and in 6% and 3% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively.

In the Phase 3 trial of subjects with decompensated cirrhosis (ASTRAL-4), lipase was assessed when amylase values were greater than or equal to 1.5xULN. Isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 2% of subjects treated with EPCLUSA with ribavirin for 12 weeks.

Creatine Kinase: In ASTRAL-1, isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% and 0% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively; and in 2% and 1% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively.

In the Phase 3 trial with decompensated cirrhosis (ASTRAL-4), isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of subjects treated with EPCLUSA with ribavirin for 12 weeks.

Indirect Bilirubin: Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-1/HCV coinfected subjects treated with EPCLUSA and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of EPCLUSA without dose adjustment or treatment interruption of either EPCLUSA or HIV antiretroviral agents.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of sofosbuvir. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiated treatment with sofosbuvir in combination with another HCV direct-acting antiviral *[see Warnings and Precautions (5.2) and Drug Interactions (7.3)].*

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect EPCLUSA

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. In vitro, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

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 decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*. EPCLUSA may be coadministered with P-gp, BCRP, and CYP inhibitors.

7.2 Potential for EPCLUSA to Affect Other Drugs

Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. Coadministration of EPCLUSA with drugs that are substrates of these transporters may increase the exposure of such drugs.

7.3 Established and Potentially Significant Drug Interactions

Table 2 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either EPCLUSA, the components of EPCLUSA (sofosbuvir and velpatasvir) as individual agents, or are predicted drug interactions that may occur with EPCLUSA *[see Warnings and Precautions (5.2, 5.3) and Clinical Pharmacology (12.3)]*.

Table 2 Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Acid Reducing Agents:	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		Separate antacid and EPCLUSA administration by 4 hours.
H_2-receptor antagonists[c] (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., omeprazole)		Coadministration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied.
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended; if coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.
digoxin[c]	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when coadministered with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: topotecan	↑ topotecan	Coadministration is not recommended.

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Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c] rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals: efavirenz[c]	↓ velpatasvir	Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving EPCLUSA concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Herbal Supplements: St. John's wort *(Hypericum perforatum)*	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: rosuvastatin[c]	↑ rosuvastatin	Coadministration of EPCLUSA with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg.
atorvastatin	↑ atorvastatin	Coadministration of EPCLUSA with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

DF = disoproxil fumarate.
a. This table is not all inclusive.
b. ↓ = decrease, ↑ = increase.
c. These interactions have been studied in healthy adults.

7.4 Drugs without Clinically Significant Interactions with EPCLUSA

Based on drug interaction studies conducted with the components of EPCLUSA (sofosbuvir or velpatasvir) or EPCLUSA, no clinically significant drug interactions have been observed with the following drugs *[see Clinical Pharmacology (12.3)]:*

- 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. See Table 2 for use of EPCLUSA with certain HIV antiretroviral regimens *[see Drug Interactions (7.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

If EPCLUSA is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on ribavirin-associated risks of use during pregnancy.

No adequate human data are available to establish whether or not EPCLUSA poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of EPCLUSA (sofosbuvir or velpatasvir) at exposures greater than those in humans at the recommended human dose (RHD) *[see Data]*. During organogenesis in the mouse, rat, and rabbit, systemic exposures (AUC) to velpatasvir were approximately 31 (mice), 6 (rats), and 0.4 (rabbits) times the exposure in humans at the RHD, while exposures to the predominant circulating metabolite of sofosbuvir (GS-331007) were approximately 4 (rats) and 10 (rabbits) times the exposure in humans at the RHD. In rat pre/postnatal development studies, maternal systemic exposures (AUC) to velpatasvir and GS-331007 were approximately 5 times the exposures of each component in humans at the RHD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Sofosbuvir: Sofosbuvir was administered orally to pregnant rats (up to 500 mg/kg/day) and rabbits (up to 300 mg/kg/day) on gestation days 6 to 18 and 6 to 19, respectively, and also to rats (oral doses up to 500 mg/kg/day) on gestation day 6 to lactation/post-partum day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. The systemic exposures (AUC) of the predominant circulating metabolite of sofosbuvir (GS-331007) during gestation were approximately 4 (rats) and 10 (rabbits) times the exposure in humans at the RHD.

Velpatasvir: Velpatasvir was administered orally to pregnant mice (up to 1000 mg/kg/day), rats (up to 200 mg/kg/day) and rabbits (up to 300 mg/kg/day) on gestation days 6 to 15, 6 to 17, and 7 to 20, respectively, and also to rats (oral doses up to 200 mg/kg) on gestation day 6 to lactation/post-partum day 20. No significant effects on embryo-fetal (mice, rats, and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. The systemic exposures (AUC) of velpatasvir during gestation were approximately 31 (mice), 6 (rats), and 0.4 (rabbits) times the exposure in humans at the RHD.

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8.2 Lactation

Risk Summary

It is not known whether the components of EPCLUSA and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats administered sofosbuvir, without effect on nursing pups. When administered to lactating rats, velpatasvir was detected in the milk of lactating rats and in the plasma of nursing pups without effects on the nursing pups *[see Data]*.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EPCLUSA and any potential adverse effects on the breastfed child from EPCLUSA or from the underlying maternal condition.

If EPCLUSA is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use during lactation.

Data

Sofosbuvir: No effects of sofosbuvir on growth and postnatal development were observed in nursing pups at the highest dose tested in rats. Maternal systemic exposure (AUC) to the predominant circulating metabolite of sofosbuvir (GS-331007) was approximately 5 times the exposure in humans at the RHD, with exposure of approximately 2% that of maternal exposure observed in nursing pups on lactation day 10. In a lactation study, sofosbuvir metabolites (primarily GS-331007) were excreted into the milk of lactating rats following administration of a single oral dose of sofosbuvir (20 mg/kg) on lactation day 2, with milk concentrations of approximately 10% that of maternal plasma concentrations observed 1 hour post-dose.

Velpatasvir: No effects of velpatasvir on growth and postnatal development were observed in nursing pups at the highest dose tested in rats. Maternal systemic exposure (AUC) to velpatasvir was approximately 5 times the exposure in humans at the RHD. Velpatasvir was present in the milk (approximately 173% that of maternal plasma concentrations) of lactating rats following a single oral dose of velpatasvir (30 mg/kg), and systemic exposure (AUC) in nursing pups was approximately 4% that of maternal exposure on lactation day 10.

8.3 Females and Males of Reproductive Potential

If EPCLUSA is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

8.4 Pediatric Use

Safety and effectiveness of EPCLUSA have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials of EPCLUSA included 156 subjects aged 65 and over (12% of total number of subjects in the Phase 3 clinical trials). No overall differences in safety or

effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of EPCLUSA is warranted in geriatric patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dosage adjustment of EPCLUSA is required for patients with mild or moderate renal impairment. The safety and efficacy of EPCLUSA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. Refer to ribavirin prescribing information regarding use of ribavirin in patients with renal impairment.

8.7 Hepatic Impairment

No dosage adjustment of EPCLUSA is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)].*

Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with EPCLUSA and ribavirin *[see Adverse Reactions (6.1)].*

10 OVERDOSAGE

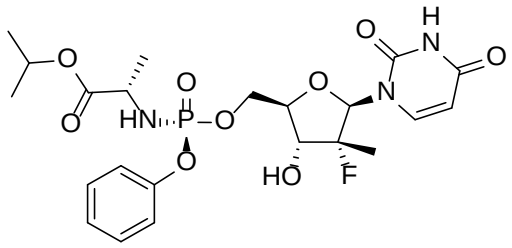
No specific antidote is available for overdose with EPCLUSA. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with EPCLUSA consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Hemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Hemodialysis is unlikely to result in significant removal of velpatasvir since velpatasvir is highly bound to plasma protein.

11 DESCRIPTION

EPCLUSA is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor and velpatasvir is an NS5A inhibitor.

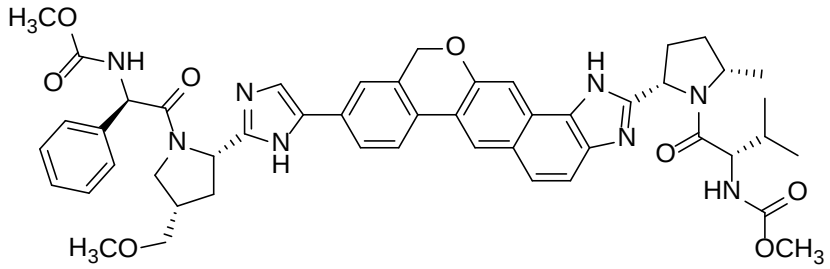
Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir. The tablets include the following inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Sofosbuvir: The IUPAC name for sofosbuvir is (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37 ^{o}C and is slightly soluble in water.

Velpatasvir: The IUPAC name for velpatasvir is Methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-*d*]imidazol-9-yl}-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0. It has the following structural formula:



Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

EPCLUSA is a fixed-dose combination of sofosbuvir and velpatasvir which are direct-acting antiviral agents against the hepatitis C virus *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of sofosbuvir 400 mg (recommended dosage) and 1200 mg (3 times the recommended dosage) on QTc interval was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT trial. At a dose 3 times the recommended dose, sofosbuvir does not prolong QTc to any clinically relevant extent.

The effect of velpatasvir 500 mg (5 times the recommended dosage) was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT trial. At a dose 5 times the

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recommended dose, velpatasvir does not prolong QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetic properties of the components of EPCLUSA are provided in Table 3. The multiple dose pharmacokinetic parameters of sofosbuvir and its metabolite, GS-331007, and velpatasvir are provided in Table 4.

Table 3 Pharmacokinetic Properties of the Components of EPCLUSA

	Sofosbuvir	Velpatasvir
Absorption		
T_{max} (h)	0.5–1	3
Effect of moderate meal (relative to fasting)[a]	↑ 60%	↑ 34%
Effect of high fat meal (relative to fasting)[a]	↑ 78%	↑ 21%
Distribution		
% Bound to human plasma proteins	61–65	>99.5
Blood-to-plasma ratio	0.7	0.52–0.67
Metabolism		
Metabolism	Cathepsin A CES1 HINT1	CYP2B6 CYP2C8 CYP3A4
Elimination		
Major route of elimination	SOF: metabolism GS-331007[b]: glomerular filtration and active tubular secretion	Biliary excretion as parent (77%)
$t_{1/2}$ (h)[c]	SOF: 0.5 GS-331007[b]: 25	15
% Of dose excreted in urine[d]	80[e]	0.4
% Of dose excreted in feces[d]	14	94

CES1 = carboxylesterase 1; HINT1 = histidine triad nucleotide-binding protein 1.

a. Values refer to mean systemic exposure. Moderate meal = ~600 kcal, 30% fat; high fat meal = ~800 kcal, 50% fat. EPCLUSA can be taken with or without food.
b. GS-331007 is the primary circulating nucleoside metabolite of SOF.
c. $t_{1/2}$ values refer to median terminal plasma half-life.
d. Single dose administration of [^{14}C] SOF or [^{14}C] VEL in mass balance studies.
e. Predominantly as GS-331007.

Table 4 Multiple Dose Pharmacokinetic Parameters of Sofosbuvir and its Metabolite, GS-331007, and Velpatasvir Following Oral Administration of EPCLUSA in HCV-Infected Adults

Parameter Mean (%CV)	Sofosbuvir[a]	GS-331007[b]	Velpatasvir[c]
C_{max} (nanogram per mL)	567 (30.7)	898 (26.7)	259 (54.3)
AUC_{tau} (nanogram•hr per mL)	1268 (38.5)	14372 (28.0)	2980 (51.3)
C_{trough} (nanogram per mL)	NA	NA	42 (67.3)

CV = coefficient of variation; NA = not applicable.

a. From Population PK analysis, N = 666
b. From Population PK analysis, N = 1029
c. From Population PK analysis, N = 1025

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Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and subjects with HCV infection. Relative to healthy subjects (N=331), velpatasvir AUC_{0-24} and C_{max} were 37% lower and 42% lower, respectively, in HCV-infected subjects.

Velpatasvir AUC increases in a greater than proportional manner from 5 to 50 mg and in a less than proportional manner from 50 to 450 mg in healthy volunteers. However, velpatasvir exhibited more than or near dose-proportional increase in exposures 25 mg to 150 mg in HCV-infected patients when coadministered with sofosbuvir. Sofosbuvir and GS-331007 AUCs are near dose-proportional over the dose range of 200 mg to 1200 mg.

Specific Populations

Pediatric Patients: The pharmacokinetics of sofosbuvir or velpatasvir in pediatric patients has not been established *[see Use in Specific Populations (8.4)]*.

Geriatric Patients: Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 82 years) analyzed, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007, or velpatasvir *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment:

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR between 50 to less than 80 mL/min/1.73 m^2), moderate (eGFR between 30 to less than 50 mL/min/1.73 m^2), severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR greater than 80 mL/min/1.73 m^2), the sofosbuvir AUC_{0-inf} was 61%, 107%, and 171% higher in subjects with mild, moderate, and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88%, and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir and GS-331007 AUC_{0-inf} was 28% and 1280% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after hemodialysis, respectively. A 4 hour hemodialysis session removed approximately 18% of administered dose *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].*

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with severe renal impairment (eGFR less than 30 mL/min by Cockcroft-Gault). No clinically relevant differences in velpatasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.

Patients with Hepatic Impairment:

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C, respectively). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects

indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007 *[see Use in Specific Populations (8.7)]*.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in subjects with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of velpatasvir *[see Use in Specific Populations (8.7)]*.

Race: Population pharmacokinetics analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposure of sofosbuvir, GS-331007, or velpatasvir.

Gender: Population pharmacokinetics analysis in HCV-infected subjects indicated that gender had no clinically relevant effect on the exposure of sofosbuvir, GS-331007, or velpatasvir.

Drug Interaction Studies

After oral administration of EPCLUSA, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction (hydrolysis followed by sequential phosphorylation) to form the pharmacologically active triphosphate. In clinical pharmacology studies, both sofosbuvir and the primary circulating metabolite GS-331007 (dephosphorylated nucleotide metabolite) were monitored for purposes of pharmacokinetic analyses.

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Velpatasvir is also transported by OATP1B1 and OATP1B3. In vitro, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed. Inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of EPCLUSA *[see Warnings and Precautions (5.3) and Drug Interactions (7.3)]*. Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and/or velpatasvir plasma concentrations without increasing GS-331007 plasma concentration. Drugs that inhibit CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir.

Velpatasvir is an inhibitor of drug transporter P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1, and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant concentration, velpatasvir is not an inhibitor of hepatic transporters OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OCT1 and GS-331007 is not an inhibitor of OAT1, OAT3,

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OCT2, and MATE1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

The effects of coadministered drugs on the exposure of sofosbuvir, GS-331007, and velpatasvir are shown in Table 5. The effects of sofosbuvir, velpatasvir, or EPCLUSA on the exposure of coadministered drugs are shown in Table 6.

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir, GS-331007, and Velpatasvir in the Presence of the Coadministered Drug[a]

Coadmini-stered Drug	Dose of Coadmini-stered Drug (mg)	SOF Dose (mg)	VEL Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007, and Velpatasvir PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF	300/100 + 200/300 once daily	400 once daily	100 once daily	24	sofosbuvir	1.12 (0.97, 1.29)	1.22 (1.12, 1.33)	NA
					GS-331007	1.21 (1.12, 1.29)	1.32 (1.27, 1.36)	1.42 (1.37, 1.49)
					velpatasvir	1.55 (1.41, 1.71)	2.42 (2.23, 2.64)	4.01 (3.57, 4.50)
Cyclosporine	600 single dose	400 single dose	ND	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
		ND	100 single dose	12	velpatasvir	1.56 (1.22, 2.01)	2.03 (1.51, 2.71)	NA
Darunavir/ ritonavir + emtricitabine/ tenofovir DF	800/100 + 200/300 once daily	400 once daily	100 once daily	29	sofosbuvir	0.62 (0.54, 0.71)	0.72 (0.66, 0.80)	NA
					GS-331007	1.04 (0.99, 1.08)	1.13 (1.08, 1.18)	1.13 (1.06, 1.19)
					velpatasvir	0.76 (0.65, 0.89)	0.84 (0.72, 0.98)	1.01 (0.87, 1.18)
Efavirenz/ emtricitabine/ tenofovir DF[b]	600/200/300 once daily	400 once daily	100 once daily	14	sofosbuvir	1.38 (1.14, 1.67)	0.97 (0.83, 1.14)	NA
					GS-331007	0.86 (0.80, 0.93)	0.90 (0.85, 0.96)	1.01 (0.95, 1.07)
					velpatasvir	0.53 (0.43, 0.64)	0.47 (0.39, 0.57)	0.43 (0.36, 0.52)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[c]	150/150/200/10 once daily	400 once daily	100 once daily	23	sofosbuvir	1.23 (1.07, 1.42)	1.37 (1.24, 1.52)	NA
					GS-331007	1.29 (1.25, 1.33)	1.48 (1.43, 1.53)	1.58 (1.52, 1.65)
					velpatasvir	1.30 (1.17, 1.45)	1.50 (1.35, 1.66)	1.60 (1.44, 1.78)

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Elvitegravir/ cobicistat/ emtricitabine/ tenofovir DF[d]	150/150/200/300 once daily	400 once daily	100 once daily	24	sofosbuvir	1.01 (0.85, 1.19)	1.24 (1.13, 1.37)	NA
					GS-331007	1.13 (1.07, 1.18)	1.35 (1.30, 1.40)	1.45 (1.38, 1.52)
					velpatasvir	1.05 (0.93, 1.19)	1.19 (1.07, 1.34)	1.37 (1.22, 1.54)
Famotidine	40 single dose simultaneously with EPCLUSA	400 single dose	100 single dose	60	sofosbuvir	0.92 (0.82, 1.05)	0.82 (0.74, 0.91)	NA
					GS-331007	0.84 (0.78, 0.89)	0.94 (0.91, 0.98)	NA
					velpatasvir	0.80 (0.70, 0.91)	0.81 (0.71, 0.91)	NA
	40 single dose 12 hours prior to EPCLUSA			60	sofosbuvir	0.77 (0.68, 0.87)	0.80 (0.73, 0.88)	NA
					GS-331007	1.20 (1.13, 1.28)	1.04 (1.01, 1.08)	NA
					velpatasvir	0.87 (0.76, 1.00)	0.85 (0.74, 0.97)	NA
Ketoconazole	200 twice daily	ND	100 single dose	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA
Lopinavir/ ritonavir + emtricitabine/ tenofovir DF	4x200/50 + 200/300 once daily	400 once daily	100 once daily	24	sofosbuvir	0.59 (0.49, 0.71)	0.71 (0.64, 0.78)	NA
					GS-331007	1.01 (0.98, 1.05)	1.15 (1.09, 1.21)	1.15 (1.07, 1.25)
					velpatasvir	0.70 (0.59, 0.83)	1.02 (0.89, 1.17)	1.63 (1.43, 1.85)
Methadone	30 to 130 daily	400 once daily	ND	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA
Omeprazole	20 once daily simultaneously with EPCLUSA	400 single dose fasted	100 single dose fasted	60	sofosbuvir	0.66 (0.55, 0.78)	0.71 (0.60, 0.83)	NA
					GS-331007	1.18 (1.10, 1.26)	1.00 (0.95, 1.05)	NA
					velpatasvir	0.63 (0.50, 0.78)	0.64 (0.52, 0.79)	NA
	20 once daily 12 hours prior to EPCLUSA	400 single dose fasted	100 single dose fasted	60	sofosbuvir	0.55 (0.47, 0.64)	0.56 (0.49, 0.65)	NA
					GS-331007	1.26 (1.18, 1.34)	0.97 (0.94, 1.01)	NA
					velpatasvir	0.43 (0.35, 0.54)	0.45 (0.37, 0.55)	NA
	20 once daily 2 hours prior to EPCLUSA	400 single dose fed[e]	100 single dose fed[e]	40	sofosbuvir	0.84 (0.68, 1.03)	1.08 (0.94, 1.25)	NA
					GS-331007	0.94 (0.88, 1.02)	0.99 (0.96, 1.03)	NA
					velpatasvir	0.52 (0.43, 0.64)	0.62 (0.51, 0.75)	NA
	20 once daily 4 hours after	400 single	100 single	38	sofosbuvir	0.79	1.05	NA

	EPCLUSA	dose fed[e]	dose fed[e]			(0.68, 0.92)	(0.94, 1.16)	
					GS-331007	0.91 (0.85, 0.98)	0.99 (0.95, 1.02)	NA
					velpatasvir	0.67 (0.58, 0.78)	0.74 (0.63, 0.86)	NA
	40 once daily 4 hours after EPCLUSA	400 single dose fed[e]	100 single dose fed[e]	40	sofosbuvir	0.70 (0.57, 0.87)	0.91 (0.76, 1.08)	NA
					GS-331007	1.01 (0.96, 1.07)	0.99 (0.94, 1.03)	NA
					velpatasvir	0.44 (0.34, 0.57)	0.47 (0.37, 0.60)	NA
Rifampin	600 once daily	400 single dose	ND	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA
		ND	100 single dose	12	velpatasvir	0.29 (0.23, 0.37)	0.18 (0.15, 0.22)	NA
	600 single dose	ND	100 single dose	12	velpatasvir	1.28 (1.05, 1.56)	1.46 (1.17, 1.83)	NA
Tacrolimus	5 single dose	400 single dose	ND	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available/not applicable, ND = not dosed, DF = disoproxil fumarate.
a. All interaction studies conducted in healthy volunteers.
b. Administered as ATRIPLA (efavirenz, emtricitabine, and tenofovir DF fixed-dose combination).
c. Administered as GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fixed-dose combination).
d. Administered as STRIBILD (elvitegravir, cobicistat, emtricitabine, and tenofovir DF fixed-dose combination).
e. EPCLUSA was administered under fasted conditions in the reference arms.

No effect on the pharmacokinetic parameters of sofosbuvir, GS-331007, or velpatasvir was observed with dolutegravir; the combination of emtricitabine, rilpivirine, and tenofovir DF; emtricitabine; raltegravir; or tenofovir DF.

Table 6 Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir, Velpatasvir, or EPCLUSA[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	SOF Dose (mg)	VEL Dose (mg)	N	Mean Ratio (90% CI) of Coadministered Drug PK With/Without Sofosbuvir, Velpatasvir, or EPCLUSA No Effect=1.00		
					C_{max}	AUC	C_{min}
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF[b]	atazanavir 300 once daily	400 once daily	100 once daily	24	1.09 (1.00, 1.19)	1.20 (1.10, 1.31)	1.39 (1.20, 1.61)
	ritonavir 100 once daily				0.89 (0.82, 0.97)	0.97 (0.89, 1.05)	1.29 (1.15, 1.44)
	emtricitabine 200				1.01	1.02	1.06

	once daily				(0.96, 1.06)	(0.99, 1.04)	(1.02, 1.11)
	tenofovir DF 300 once daily				1.55 (1.43, 1.68)	1.30 (1.24, 1.36)	1.39 (1.31, 1.48)
Darunavir/ ritonavir + emtricitabine/ tenofovir DF[c]	darunavir 800 once daily	400 once daily	100 once daily	29	0.90 (0.86, 0.95)	0.92 (0.87, 0.98)	0.87 (0.79, 0.95)
	ritonavir 100 once daily				1.07 (0.97, 1.17)	1.12 (1.05, 1.19)	1.09 (1.02, 1.15)
	emtricitabine 200 once daily				1.05 (1.01, 1.08)	1.05 (1.02, 1.08)	1.04 (0.98, 1.09)
	tenofovir DF 300 once daily				1.55 (1.45, 1.66)	1.39 (1.33, 1.44)	1.52 (1.45, 1.59)
Digoxin	0.25 single dose	ND	100	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA
Efavirenz/ emtricitabine/ tenofovir DF[d]	efavirenz 600 once daily	400 once daily	100 once daily	15	0.81 (0.74, 0.89)	0.85 (0.80, 0.91)	0.90 (0.85, 0.95)
	emtricitabine 200 once daily				1.07 (0.98, 1.18)	1.07 (1.00, 1.14)	1.10 (0.97, 1.25)
	tenofovir DF 300 once daily				1.77 (1.53, 2.04)	1.81 (1.68, 1.94)	2.21 (2.00, 2.43)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[e]	elvitegravir 150 once daily	400 once daily	100 once daily	24	0.87 (0.80, 0.94)	0.94 (0.88, 1.00)	1.08 (0.97, 1.20)
	cobicistat 150 once daily				1.16 (1.09, 1.23)	1.30 (1.23, 1.38)	2.03 (1.67, 2.48)
	emtricitabine 200 once daily				1.02 (0.97, 1.06)	1.01 (0.98, 1.04)	1.02 (0.97, 1.07)
	tenofovir alafenamide 10 once daily				0.80 (0.68, 0.94)	0.87 (0.81, 0.94)	NA
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir DF[f]	elvitegravir 150 once daily	400 once daily	100 once daily	24	0.93 (0.86, 1.00)	0.93 (0.87, 0.99)	0.97 (0.91, 1.04)
	cobicistat 150 once daily				1.11 (1.06, 1.17)	1.23 (1.17, 1.29)	1.71 (1.54, 1.90)
	emtricitabine 200 once daily				1.02 (0.97, 1.08)	1.01 (0.98, 1.04)	1.06 (1.01, 1.11)
	tenofovir DF 300 once daily				1.36 (1.25, 1.47)	1.35 (1.29, 1.42)	1.45 (1.39, 1.51)
Emtricitabine/ rilpivirine/ tenofovir DF[g]	emtricitabine 200 once daily	400 once daily	100 once daily	24	0.95 (0.90, 1.00)	0.99 (0.97, 1.02)	1.05 (0.99, 1.11)
	rilpivirine 25 once daily				0.93 (0.88, 0.98)	0.95 (0.90, 1.00)	0.96 (0.90, 1.03)
	tenofovir DF 300 once daily				1.44 (1.33, 1.55)	1.40 (1.34, 1.46)	1.84 (1.76, 1.92)
Norelgestromin	norgestimate 0.180/0.215/0.25/ ethinyl estradiol 0.025 once daily	ND	100 once daily	13	0.97 (0.88, 1.07)	0.90 (0.82, 0.98)	0.92 (0.83, 1.03)
		400 once daily	ND	15	1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel		ND	100 once	13	0.96 (0.78, 1.19)	0.91 (0.73, 1.15)	0.92 (0.73, 1.18)

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			daily				
		400 once daily	ND	15	1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol		ND	100 once daily	12	1.39 (1.17, 1.66)	1.04 (0.87, 1.24)	0.83 (0.65, 1.06)
		400 once daily	ND	15	1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Pravastatin	pravastatin 40 single dose	ND	100 once daily	18	1.28 (1.08, 1.52)	1.35 (1.18, 1.54)	NA
Rosuvastatin	rosuvastatin 10 single dose	ND	100 once daily	18	2.61 (2.32, 2.92)	2.69 (2.46, 2.94)	NA
Raltegravir + emtricitabine/ tenofovir DF	emtricitabine 200 once daily	400 once daily	100 once daily	30	1.08 (1.04, 1.12)	1.05 (1.03, 1.07)	1.02 (0.97, 1.08)
	tenofovir DF 300 once daily				1.46 (1.39, 1.54)	1.40 (1.34, 1.45)	1.70 (1.61, 1.79)
	raltegravir 400 twice daily				1.03 (0.74, 1.43)	0.97 (0.73, 1.28)	0.79 (0.42, 1.48)
Tacrolimus	5 single dose	400 single dose	ND	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA

NA = not available/not applicable, ND = not dosed, DF = disoproxil fumarate.
a. All interaction studies conducted in healthy volunteers.
b. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
c. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
d. Administered as ATRIPLA (efavirenz, emtricitabine, and tenofovir DF fixed-dose combination).
e. Administered as GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fixed-dose combination).
f. Administered as STRIBILD (elvitegravir, cobicistat, emtricitabine, and tenofovir DF fixed-dose combination).
g. Administered as COMPLERA (emtricitabine, rilpivirine, and tenofovir DF fixed-dose combination).

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with EPCLUSA (dolutegravir or lopinavir/ritonavir) or its components sofosbuvir (cyclosporine or methadone) or velpatasvir (cyclosporine).

12.4 Microbiology

Mechanism of Action

Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC_{50} value ranging from 0.36 to 3.3 micromolar. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Velpatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Antiviral Activity

The EC_{50} values of sofosbuvir and velpatasvir against full-length or chimeric replicons encoding NS5B and NS5A sequences from the laboratory strains are presented in Table 7. The EC_{50} values of sofosbuvir and velpatasvir against clinical isolates are presented in Table 8.

Table 7 Activity of Sofosbuvir and Velpatasvir Against Full Length or Chimeric Laboratory Replicons

Replicon Genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]
1a	40	0.014
1b	110	0.016
2a	50	0.005–0.016[c]
2b	15[b]	0.002–0.006[c]
3a	50	0.004
4a	40	0.009
4d	33.4	0.004
5a	15[b]	0.021–0.054[d]
6a	14–25[b]	0.006–0.009
6e	NA	0.130[d]

NA = not available.
a. Mean value from multiple experiments of same laboratory replicon.
b. Stable chimeric 1b replicons carrying NS5B genes from genotype 2b, 5a, or 6a were used for testing.
c. Data from various strains of full-length NS5A replicons or chimeric NS5A replicons carrying full-length NS5A genes that contain L31 or M31 polymorphisms.
d. Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

Table 8 Activity of Sofosbuvir and Velpatasvir Against Transient Replicons Containing NS5A or NS5B from Clinical Isolates

Replicon Genotype	Replicons Containing NS5B from Clinical Isolates		Replicons Containing NS5A from Clinical Isolates	
	Number of clinical isolates	Median sofosbuvir EC_{50}, nM (range)	Number of clinical isolates	Median velpatasvir EC_{50}, nM (range)
1a	67	62 (29–128)	23	0.019 (0.011–0.078)
1b	29	102 (45–170)	34	0.012 (0.005–0.500)
2a	1	28	8	0.011 (0.006–0.364)
2b	14	30 (14–81)	16	0.002 (0.0003–0.007)
3a	106	81 (24–181)	38	0.005 (0.002–1.871)
4a	NA	NA	5	0.002 (0.001–0.004)
4d	NA	NA	10	0.007 (0.004–0.011)
4r	NA	NA	7	0.003 (0.002–0.006)

5a	NA	NA	42	0.005 (0.001–0.019)
6a	NA	NA	26	0.007 (0.0005–0.113)
6e	NA	NA	15	0.024 (0.005–0.433)

NA = not available.

Velpatasvir was not antagonistic in reducing HCV RNA levels in replicon cells when combined with sofosbuvir or interferon-α, ribavirin, an HCV NS3/4A protease inhibitor, or HCV NS5B non-nucleoside inhibitors.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a, and 6a. Reduced susceptibility to sofosbuvir was associated with the NS5B substitution S282T in all replicon genotypes examined. An M289L substitution developed along with the S282T substitution in genotype 2a, 5, and 6 replicons. Site-directed mutagenesis of the S282T substitution in replicons of genotypes 1 to 6 conferred 2- to 18-fold reduced susceptibility to sofosbuvir.

HCV genotype 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to velpatasvir were selected in cell culture. Variants developed amino acid substitutions at NS5A resistance-associated positions 24, 28, 30, 31, 32, 58, 92, and 93. Phenotypic analysis of site-directed mutant replicons of the selected NS5A substitutions showed that single and double combinations of L31V and Y93H/N in genotype 1a, the combination of L31V + Y93H in genotype 1b, Y93H/S in genotype 3a, and L31V and P32A/L/Q/R in genotype 6 conferred greater than 100-fold reduction in velpatasvir susceptibility. In the genotype 2a replicon, the single mutants F28S and Y93H showed 91-fold and 46-fold reduced susceptibility to velpatasvir, respectively. The single mutant Y93H conferred 3-fold reduced susceptibility to velpatasvir in genotype 4a replicons. Combinations of these NS5A substitutions often showed greater reductions in susceptibility to velpatasvir than single substitutions alone.

In Clinical Trials

Studies in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis

In a pooled analysis of subjects without cirrhosis or with compensated cirrhosis who received EPCLUSA for 12 weeks in Phase 3 trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3), 12 subjects (2 with genotype 1 [1a, 1c/h] and 10 with genotype 3a) qualified for resistance analysis due to virologic failure. No subjects with genotype 2, 4, 5, or 6 HCV infection experienced virologic failure.

Of the 2 genotype 1 virologic failure subjects, 1 subject had virus with emergent NS5A resistance substitution Y93N and the other had virus with emergent NS5A resistance substitutions Y93H and low-level K24M/T and L31I/V at virologic failure. The latter subject had genotype 1c/h virus at baseline harboring NS5A resistance polymorphisms (Q30R, L31M, H58P) relative to genotype 1a. No sofosbuvir NS5B nucleoside analog resistance-associated substitutions were observed at failure in the 2 subjects.

Of the 10 genotype 3a virologic failure subjects, NS5A resistance substitution Y93H was observed in all 10 subjects at failure (7 subjects had Y93H emerge post-treatment and 3 subjects had Y93H at baseline and post-treatment). Treatment-emergent sofosbuvir NS5B substitutions L314F (n=2) and L314I (n=1) were observed at high frequency (greater than or equal to 15%) in the NS5B polymerase in 3 genotype 3a subjects who relapsed: one in the EPCLUSA group and two in the sofosbuvir plus ribavirin 24-week group. In addition, low frequency (less than 4%) treatment-emergent L314P was detected in 2 genotype 3a subjects who relapsed, including one subject in the sofosbuvir plus ribavirin 24-week group in ASTRAL-3 and one in the EPCLUSA group in ASTRAL-4. The clinical significance of this substitution is unknown.

Studies in Subjects with Decompensated Cirrhosis

In the ASTRAL-4 trial in subjects with decompensated cirrhosis who received EPCLUSA with ribavirin for 12 weeks, 3 subjects (1 with genotype 1a and 2 with genotype 3a) qualified for resistance analysis due to virologic failure. No subjects with genotype 2 or 4 HCV infection who received EPCLUSA with ribavirin for 12 weeks experienced virologic failure.

The genotype 1 virologic failure subject had no NS5A or NS5B resistance substitutions at failure.

The 2 genotype 3a virologic failure subjects had the NS5A resistance substitutions Y93H and either low-level M28V or S38P emerge at failure. One of these subjects also developed low levels (less than 5%) of NS5B nucleoside analog inhibitor resistance substitutions N142T and E237G at failure.

In the ASTRAL-4 trial, 2 subjects treated with EPCLUSA for 12 or 24 weeks without ribavirin had emergent sofosbuvir NS5B resistance-associated substitutions S282T at low levels (less than 5%) along with L159F. EPCLUSA for 12 or 24 weeks without ribavirin is not recommended in patients with decompensated cirrhosis.

Persistence of Resistance-Associated Substitutions

No data are available on the persistence of sofosbuvir or velpatasvir resistance-associated substitutions. NS5A resistance-associated substitutions observed with administration of other NS5A inhibitors have been found to persist for longer than 1 year in most patients. The long-term clinical impact of the emergence or persistence of virus containing sofosbuvir or velpatasvir resistance-associated substitutions is unknown.

Effect of Baseline HCV Polymorphisms on Treatment Response

Analyses were conducted to explore the association between relapse rates and pre-existing baseline NS5A resistance-associated polymorphisms (RAPs) (any change from reference at NS5A amino acid positions 24, 28, 30, 31, 58, 92, or 93) identified by population or deep sequencing analysis at a sensitivity threshold of 15% or higher for subjects without cirrhosis or with compensated cirrhosis in ASTRAL-1, ASTRAL-2, and ASTRAL-3 and subjects with decompensated cirrhosis in ASTRAL-4.

Studies in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis

Among the subjects who received treatment with EPCLUSA for 12 weeks, 18% (37/209), 32% (38/117), 64% (149/232), 20% (56/274), 63% (73/115), 9% (3/34),

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and 83% (35/42) of subjects with genotype 1a, 1b, 2, 3, 4, 5, and 6 HCV, respectively, had baseline virus with NS5A RAPs.

Genotype 1: Among the 75 genotype 1 subjects who had baseline NS5A RAPs, one subject (1%) with Q30R, L31M and H58P polymorphisms at baseline and compensated cirrhosis relapsed.

Genotype 3: Among the 56 genotype 3 subjects who had baseline NS5A RAPs, 4 subjects (7%) relapsed (3 with baseline Y93H and 1 with baseline A30K). Overall, 20% (3/15) of genotype 3 subjects with the Y93H polymorphism at baseline relapsed.

For genotype 3 subjects with compensated cirrhosis, relapse rates were 33% (3/9) for subjects with baseline NS5A RAPs compared to 6% (4/71) for subjects without baseline NS5A RAPs.

Genotypes 2, 4, 5, and 6: The presence of baseline NS5A RAPs did not affect relapse rates for subjects with genotypes 2, 4, 5, and 6, because all achieved SVR12.

SVR12 was achieved in all 77 subjects who had baseline NS5B nucleoside analog inhibitor resistance polymorphisms including N142T, L159F, E/N237G, C/M289L/I, L320F/I/V, V321A/I, and S282G + V321I. The sofosbuvir NS5B nucleoside analog inhibitor resistance substitution S282T was not detected in the baseline NS5B sequence of any subject using 1% deep sequencing cutoff in Phase 3 trials.

Studies in Subjects with Decompensated Cirrhosis

In ASTRAL-4, the prevalence of NS5A RAPs at baseline was 24% (48/198), 60% (6/10), 11% (4/37), and 63% (5/8) in GT1, GT2, GT3, and GT4 HCV subjects, respectively. No subjects with genotypes 2, 4 and 6 relapsed. There were no subjects with genotype 5 in this trial.

For genotype 1 subjects, the overall relapse rates were numerically lower for the 12-week EPCLUSA with ribavirin group (2%; 1/66) compared to EPCLUSA 12-week and 24-week treatment groups. For subjects with NS5A RAPs, relapse rates were 0% (0/17) compared to 2% (1/49) for subjects without NS5A RAPs in the 12-week EPCLUSA with ribavirin containing group.

For genotype 3 subjects, overall virologic failure rates were numerically lower for the 12-week EPCLUSA with ribavirin group (15%; 2/13) compared to EPCLUSA 12-week and 24-week treatment groups. There are insufficient data to determine the impact of HCV NS5A RAPs in genotype 3 subjects with decompensated cirrhosis.

Three subjects in the EPCLUSA with ribavirin 12-week group had baseline NS5B nucleoside analog inhibitor polymorphisms (N142T and L159F) using 1% deep sequencing cutoff and all 3 subjects achieved SVR12.

Cross Resistance

Both sofosbuvir and velpatasvir were fully active against substitutions associated with resistance to other classes of direct-acting antivirals with different mechanisms of action, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. The efficacy of EPCLUSA has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Sofosbuvir: Sofosbuvir was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo mouse micronucleus assays.

Sofosbuvir was not carcinogenic in a 2-year mouse study (up to 200 mg/kg/day in males and 600 mg/kg/day in females) and in a 2-year rat study (up to 750 mg/kg/day), resulting in exposures of the predominant circulating metabolite GS-331007 of approximately 3 and 15 times (in mice) and 7 and 9 times (in rats), in males and females, respectively, the exposure in humans at the recommended human dose (RHD).

Velpatasvir: Velpatasvir was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and in vivo rat micronucleus assays.

Carcinogenicity studies of velpatasvir in mice and rats are ongoing.

Impairment of Fertility

Sofosbuvir: Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, AUC exposure to the predominant circulating metabolite GS-331007 was approximately 4 times the exposure in humans at the RHD.

Velpatasvir: Velpatasvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, velpatasvir exposure was approximately 6 times the exposure in humans at the RHD.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

Table 9 presents the clinical trial design including different treatment groups that were conducted with EPCLUSA with and without ribavirin in subjects with chronic hepatitis C (HCV) genotype 1, 2, 3, 4, 5, and 6 infection. For detailed description of trial design and recommended regimen and duration *[see Dosage and Administration (2) and Clinical Studies (14.2, 14.3)]*.

Table 9 Trials Conducted with EPCLUSA in Subjects with Genotype 1, 2, 3, 4, 5, or 6 HCV Infection

Trial	Population	EPCLUSA and Comparator Groups (Number of Subjects Treated)
ASTRAL-1	Genotype 1, 2, 4, 5, and 6 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2 TN and TE, without cirrhosis or	EPCLUSA 12 weeks (134) SOF + RBV 12 weeks (132)

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	with compensated cirrhosis	
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (277) SOF + RBV 24 weeks (275)
ASTRAL-4	Genotype 1, 2, 3, 4, 5, and 6 TN and TE, with CP class B decompensated cirrhosis	EPCLUSA 12 weeks (90) EPCLUSA + RBV 12 weeks (87) EPCLUSA 24 weeks (90)

TN = treatment-naïve subjects; TE = treatment-experienced subjects (including those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor); SOF = sofosbuvir, RBV = ribavirin; CP = Child-Pugh.

The ribavirin dosage was weight-based (1000 mg daily administered in two divided doses for subjects less than 75 kg and 1200 mg for those greater than or equal to 75 kg) and administered in two divided doses when used in combination with sofosbuvir in the ASTRAL-2 and ASTRAL-3 trials or in combination with EPCLUSA in the ASTRAL-4 trial. Ribavirin dosage adjustments were performed according to the ribavirin prescribing information. Serum HCV RNA values were measured during the clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL. Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint in all the trials. Relapse is defined as HCV RNA greater than or equal to LLOQ during the post-treatment period after having achieved HCV RNA less than LLOQ at the end of treatment. On-treatment virologic failure is defined as breakthrough, rebound, or non-response.

14.2 Clinical Trials in Subjects without Cirrhosis and Subjects with Compensated Cirrhosis

Genotype 1, 2, 4, 5, and 6 HCV Infected Adults (ASTRAL-1)

ASTRAL-1 was a randomized, double-blind, placebo-controlled trial that evaluated 12 weeks of treatment with EPCLUSA compared with 12 weeks of placebo in subjects with genotype 1, 2, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis. Subjects with genotype 1, 2, 4, or 6 HCV infection were randomized in a 5:1 ratio to treatment with EPCLUSA or placebo for 12 weeks. Subjects with genotype 5 HCV infection were enrolled to the EPCLUSA group. Randomization was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of compensated cirrhosis.

Demographics and baseline characteristics were balanced between the EPCLUSA and placebo group. Of the 740 treated subjects, the median age was 56 years (range: 18 to 82); 60% of the subjects were male; 79% were White, 9% were Black; 21% had a baseline body mass index at least 30 kg/m^2; the proportions of subjects with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5%, and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced.

Table 10 presents SVR12 and other virologic outcomes in EPCLUSA-treated subjects in the ASTRAL-1 trial by HCV genotype. No subjects in the placebo group achieved SVR12.

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Table 10 Study ASTRAL-1: Virologic Outcomes by HCV Genotype in EPCLUSA-Treated Subjects without Cirrhosis or with Compensated Cirrhosis (12 Weeks After Treatment)

	EPCLUSA 12 Weeks (N=624)							
	Total (all GTs) (N=624)	GT-1			GT-2 (N=104)	GT-4 (N=116)	GT-5 (N=35)	GT-6 (N=41)
		GT-1a (N=210)	GT-1b (N=118)	Total (N=328)				
SVR12	99% (618/624)	98% (206/210)	99% (117/118)	98% (323/328)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)
Outcome for Subjects without SVR								
On-Treatment Virologic Failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse[a]	<1% (2/623)	<1% (1/209)	1% (1/118)	1% (2/327)	0/104	0/116	0/35	0/41
Other[b]	1% (4/624)	1% (3/210)	0/118	1% (3/328)	0/104	0/116	3% (1/35)	0/41

GT = genotype; no subjects in the placebo group achieved SVR12.

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria.

Genotype 2 HCV Infected Adults (ASTRAL-2)

ASTRAL-2 was a randomized, open-label trial that evaluated 12 weeks of treatment with EPCLUSA compared with 12 weeks of treatment with SOF with ribavirin in subjects with genotype 2 HCV infection. Subjects were randomized in a 1:1 ratio to the treatment groups. Randomization was stratified by the presence or absence of compensated cirrhosis and prior treatment experience (treatment-naïve vs treatment-experienced).

Demographics and baseline characteristics were balanced across the two treatment groups. Of the 266 treated subjects, the median age was 58 years (range: 23 to 81); 59% of the subjects were male; 88% were White; 7% were Black; 33% had a baseline body mass index at least 30 kg/m^2; 62% had non-CC IL28B alleles (CT or TT); 80% had baseline HCV RNA levels at least 800,000 IU/mL; 14% had compensated cirrhosis; and 15% were treatment-experienced.

Table 11 presents SVR12 and other virologic outcomes from the ASTRAL-2 trial.

Table 11 Study ASTRAL-2: Virologic Outcomes in Subjects with Genotype 2 HCV without Cirrhosis or with Compensated Cirrhosis (12 Weeks After Treatment)

	EPCLUSA 12 Weeks (N=134)	SOF + RBV 12 Weeks (N=132)
SVR12	99% (133/134)	94% (124/132)
	Treatment difference +5.2%; 95% confidence interval (+0.2% to +10.3%)	
Outcome for subjects without SVR		
On-Treatment Virologic Failure	0/134	0/132
Relapse[a]	0/133	5% (6/132)
Other[b]	1% (1/134)	2% (2/132)

SOF = sofosbuvir; RBV = ribavirin.

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the last on-treatment assessment.

b. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria.

Genotype 3 HCV Infected Adults (ASTRAL-3)

ASTRAL-3 was a randomized, open-label trial that evaluated 12 weeks of treatment with EPCLUSA compared with 24 weeks of treatment with SOF with ribavirin in subjects with genotype 3 HCV infection. Subjects were randomized in a 1:1 ratio to the treatment groups. Randomization was stratified by the presence or absence of compensated cirrhosis and prior treatment experience (treatment-naïve vs treatment-experienced).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 552 treated subjects, the median age was 52 years (range: 19 to 76); 62% of the subjects were male; 89% were White; 9% were Asian; 20% had a baseline body mass index at least 30 kg/m^2; 61% had non-CC IL28B alleles (CT or TT); 70% had baseline HCV RNA levels at least 800,000 IU/mL; 30% had compensated cirrhosis; and 26% were treatment-experienced.

Table 12 presents SVR12 and other virologic outcomes from the ASTRAL-3 trial.

Table 12 Study ASTRAL-3: Virologic Outcomes in Subjects with Genotype 3 HCV without Cirrhosis or with Compensated Cirrhosis (12 Weeks After Treatment)

	EPCLUSA 12 Weeks (N=277)	SOF + RBV 24 Weeks (N=275)
SVR12	95% (264/277)	80% (221/275)
	Treatment difference +14.8%; 95% confidence interval (+9.6% to +20.0%)	
Outcome for subjects without SVR		
On-Treatment Virologic Failure	0/277	<1% (1/275)
Relapse[a]	4% (11/276)	14% (38/272)
Other[b]	1% (2/277)	5% (15/275)

SOF = sofosbuvir; RBV = ribavirin.

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the last on-treatment assessment.

b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria.

SVR12 for selected subgroups are presented in Table 13.

Table 13 Study ASTRAL-3: SVR12 by Prior Treatment and Presence/Absence of Compensated Cirrhosis in Subjects with Genotype 3 HCV

	EPCLUSA 12 Weeks		SOF + RBV 24 Weeks[a]	
	Treatment-Naïve (N=206)	Treatment-Experienced (N=71)	Treatment-Naïve (N=201)	Treatment-Experienced (N=69)
Without cirrhosis	98% (160/163)	94% (31/33)[b]	90% (141/156)	71% (22/31)
With compensated cirrhosis	93% (40/43)	89% (33/37)	73% (33/45)	58% (22/38)

SOF = sofosbuvir; RBV = ribavirin.

a. Five subjects with missing cirrhosis status in the SOF + RBV 24-week group were excluded from this subgroup analysis.

b. One treatment-experienced subject without cirrhosis treated with EPCLUSA had genotype 1a HCV infection at failure, indicating HCV re-infection, and is therefore excluded from this analysis.

14.3 Clinical Trials in Subjects with Decompensated Cirrhosis

ASTRAL-4 was a randomized, open-label trial in subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection and Child-Pugh B cirrhosis at screening. Subjects were randomized in a 1:1:1 ratio to treatment with EPCLUSA for 12 weeks (N=90), EPCLUSA with ribavirin for 12 weeks (N=87), or EPCLUSA for 24 weeks (N=90). Randomization was stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated subjects, the median age was 59 years (range: 40 to 73); 70% of the subjects were male; 90% were White, 6% were Black; 42% had a baseline body mass index at least 30 kg/m^2. The proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV were 78%, 4%, 15%, 3%, and less than 1% (1 subject), respectively. No subjects with

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genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; and 95% of subjects had Model for End Stage Liver Disease (MELD) score less than or equal to 15 at baseline. Although all subjects had Child-Pugh B cirrhosis at screening, 6% and 4% of subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment.

Treatment with EPCLUSA with ribavirin for 12 weeks resulted in numerically higher SVR12 rates than treatment with EPCLUSA for 12 weeks or 24 weeks. Because EPCLUSA with ribavirin for 12 weeks is the recommended dosage regimen, the results of the 12- and 24-week EPCLUSA treatment groups are not presented.

Table 14 presents the SVR12 for subjects treated with EPCLUSA with ribavirin for 12 weeks in the ASTRAL-4 trial by HCV genotype. No subjects with genotype 5 or 6 HCV were treated with EPCLUSA with ribavirin for 12 weeks.

Table 14 Study ASTRAL-4: Virologic Outcomes in Subjects with Decompensated Cirrhosis After 12 Weeks of Treatment by HCV Genotype

	EPCLUSA + RBV 12 Weeks (N=87)	
	SVR12	Virologic Failure (relapse and on-treatment failure)
Overall SVR12[a]	94% (82/87)	3% (3/87)
Genotype 1	96% (65/68)	1% (1/68)[b]
Genotype 1a	94% (51/54)	2% (1/54)[b]
Genotype 1b	100% (14/14)	0% (0/14)
Genotype 3	85% (11/13)	15% (2/13)[c]

RBV = ribavirin.

a. Includes subjects with baseline CPT C cirrhosis: all 4 subjects achieved SVR12.
b. This subject with genotype 1a experienced relapse.
c. One subject had on-treatment virologic failure; pharmacokinetic data from this subject was consistent with non-adherence.

All subjects with genotype 2 (N=4) and genotype 4 (N=2) HCV infection treated with EPCLUSA and ribavirin achieved SVR12.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each EPCLUSA tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir, is pink, diamond-shaped, film-coated, debossed with “GSI” on one side and “7916” on the other. Each bottle contains 28 tablets (NDC 61958-2201-1), polyester coil, and is closed with a child-resistant closure.

Store below 30 °C (86 ºF). Dispense only in original container.

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17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

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

Inform patients that HBV reactivation can occur in patients coinfected with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of HBV infection *[see Warnings and Precautions (5.1)]*.

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

Advise patients to seek medical evaluation immediately for symptoms of bradycardia such as near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems *[see Warnings and Precautions (5.2), Adverse Reactions (6.2), and Drug Interactions (7.3)].*

Drug Interactions

Inform patients that EPCLUSA may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products including St. John's wort *[see Warnings and Precautions (5.2, 5.3) and Drug Interactions (7)].*

Administration

Advise patients to take EPCLUSA once daily on a regular dosing schedule with or without food. Inform patients that it is important not to miss or skip doses and to take EPCLUSA for the duration that is recommended by the physician.

Pregnancy

Advise patients to avoid pregnancy during combination treatment with EPCLUSA and ribavirin and for 6 months after completion of treatment. Inform patients to notify their healthcare provider immediately in the event of a pregnancy *[see Use in Specific Populations (8.1)]*.

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Gilead Sciences, Inc.
Foster City, CA 94404

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Patient Information
EPCLUSA® (ep-KLOO-suh)
(sofosbuvir and velpatasvir)
tablets

Read this Patient Information before you start taking EPCLUSA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. **If you take EPCLUSA with ribavirin, you should also read the Medication Guide for ribavirin.**

What is EPCLUSA?

- EPCLUSA is a prescription medicine used to treat adults with chronic (lasting a long time) hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection:
  - without cirrhosis or with compensated cirrhosis
  - with advanced cirrhosis (decompensated) in combination with ribavirin
- EPCLUSA contains the two medicines: sofosbuvir and velpatasvir.

It is not known if EPCLUSA is safe and effective in children under 18 years of age.

What is the most important information I should know about EPCLUSA?

EPCLUSA can cause serious side effects, including,

Hepatitis B virus reactivation: Before starting treatment with EPCLUSA, your healthcare provider will do blood tests to check for hepatitis B virus infection. If you have ever had hepatitis B virus infection, the hepatitis B virus could become active again during or after treatment of hepatitis C virus with EPCLUSA. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems including liver failure and death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop taking EPCLUSA.

For more information about side effects, see the section "What are the possible side effects of EPCLUSA?"

What should I tell my healthcare provider before taking EPCLUSA?

Before taking EPCLUSA, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had hepatitis B virus infection
- have liver problems other than hepatitis C infection
- have severe kidney problems or you are on dialysis
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if EPCLUSA will harm your unborn baby.
  - Females who take EPCLUSA in combination with ribavirin should avoid becoming pregnant during treatment and for 6 months after stopping treatment. Call your healthcare provider right away if you think you may be pregnant or become pregnant during treatment with EPCLUSA in combination with ribavirin.
  - **Males and females who take EPCLUSA in combination with ribavirin should also read the ribavirin Medication Guide for important pregnancy, contraception, and infertility information.**
- are breastfeeding or plan to breastfeed. It is not known if EPCLUSA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take EPCLUSA.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. EPCLUSA and other medicines may affect each other. This can cause you to have too much or not enough EPCLUSA or other medicines in your body. This may affect the way EPCLUSA or your other medicines work, or may cause side effects.

Keep a list of your medicines to show your healthcare provider and pharmacist.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with EPCLUSA.
- **Tell your healthcare provider if you take any medicines containing tenofovir disoproxil**

fumarate (ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®, VIREAD®).

Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take EPCLUSA with other medicines.

How should I take EPCLUSA?

- Take EPCLUSA exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking EPCLUSA without first talking with your healthcare provider.
- Take 1 EPCLUSA tablet each day.
- Take EPCLUSA with or without food.
- It is important that you do not miss or skip doses of EPCLUSA during treatment.
- If you take too much EPCLUSA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of EPCLUSA?

EPCLUSA can cause serious side effects, including:

- Hepatitis B virus reactivation. See "What is the most important information I should know about EPCLUSA?"
- **Slow heart rate (bradycardia).** EPCLUSA treatment may result in slowing of the heart rate along with other symptoms when taken with amiodarone (Cordarone®, Nexterone®, Pacerone®), a medicine used to treat certain heart problems. In some cases bradycardia has led to death or the need for a heart pacemaker when amiodarone is taken with medicines similar to EPCLUSA that are a combination of sofosbuvir and another antiviral medicine. Get medical help right away if you take amiodarone with EPCLUSA and get any of the following symptoms:
  - fainting or near-fainting
  - dizziness or lightheadedness
  - not feeling well
  - weakness
  - extreme tiredness
  - shortness of breath
  - chest pains
  - confusion
  - memory problems
- The most common side effects of EPCLUSA include headache and tiredness.
- Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
- These are not all the possible side effects of EPCLUSA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EPCLUSA?

- Store EPCLUSA at room temperature below 86 ^{o}F (30 ^{o}C).
- Keep EPCLUSA in its original container.
- Do not use EPCLUSA if the seal over the bottle opening is broken or missing.

Keep EPCLUSA and all medicines out of the reach of children.

General information about the safe and effective use of EPCLUSA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EPCLUSA for a condition for which it was not prescribed. Do not give EPCLUSA to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information about EPCLUSA, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about EPCLUSA that is written for health professionals.

For more information, call 1-800-445-3235 or go to www.epclusainfo.com.

What are the ingredients in EPCLUSA?

Active ingredients: sofosbuvir and velpatasvir

Inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The tablet film-coat contains: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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