Product Monograph

INCLUDING PATIENT MEDICATION INFORMATION

Pr EPCLUSA™

(sofosbuvir/velpatasvir) Tablets

400 mg/100 mg

Antiviral Agent

Gilead Sciences Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3
Canada

www.gilead.ca

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EPCLUSA™
sofosbuvir/velpatasvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 400 mg sofosbuvir/100 mg velpatasvir	Not applicable

*For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

EPCLUSA (sofosbuvir/velpatasvir) is indicated:

- for the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis
- in combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection in adults with decompensated cirrhosis.

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of younger patients across treatment groups. EPCLUSA can be administered in geriatric patients (see **ACTION AND CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age)

Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

EPCLUSA is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

When EPCLUSA is used in combination with ribavirin, the contraindications to ribavirin are also applicable to the combination regimen. Refer to the Product Monograph containing information on ribavirin for a list of contraindications for ribavirin.

WARNINGS AND PRECAUTIONS

General

Treatment with EPCLUSA should be initiated and monitored by a physician experienced in the management of chronic hepatitis C virus (HCV) infection.

Data to support the treatment of patients with decompensated cirrhosis who are infected with HCV genotype 2 or genotype 4 are limited, and there are no data for genotype 5 and genotype 6 HCV infected patients with decompensated cirrhosis. The indication for treatment of these patients is based on extrapolation of relevant clinical and *in vitro* data (see **CLINICAL TRIALS** and **MICROBIOLOGY**).

EPCLUSA should not be administered concurrently with other medicinal products containing sofosbuvir.

Use with Potent P-gp Inducers and/or Moderate to Potent Inducers of CYP

Medicinal products that are potent P-glycoprotein (P-gp) inducers and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 [e.g. rifampin, St. John's wort (*Hypericum perforatum*) and carbamazepine] may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir leading to reduced therapeutic effect of EPCLUSA and potential loss of virologic response. These agents should not be used with EPCLUSA (see **DRUG INTERACTIONS**).

Cardiovascular

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

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, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Hepatic

The safety and efficacy of EPCLUSA has not been established in patients with severe hepatic impairment (Child-Pugh Class C) (see **ACTION AND CLINICAL PHARMACOLOGY**).

Monitoring of liver function including direct bilirubin is recommended in patients with decompensated cirrhosis.

Renal

The safety and efficacy of EPCLUSA has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY)**.

Resistance

The efficacy of EPCLUSA has not been established in patients who have previously failed treatment with other regimens that include a NS5A inhibitor (see **MICROBIOLOGY, Cross Resistance**).

Sexual Function/Reproduction

There are no data on the effect of sofosbuvir and velpatasvir on human fertility. No effects on fertility were observed in animal studies for sofosbuvir and velpatasvir (see **TOXICOLOGY**).

Special Populations

Pregnant Women

Use without Ribavirin

Pregnancy should be avoided while taking EPCLUSA as there are no data on the use of EPCLUSA in pregnant women. EPCLUSA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their health care provider immediately in the event of a pregnancy.

No effects on pre- or post-natal development were observed in animal reproduction studies at the highest doses of sofosbuvir tested. In the rat and rabbit embryo fetal studies, and the rat pre/post-natal study, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 5-fold, 14-fold, and 6-fold the exposure in humans at the recommended clinical dose, respectively.

No effects on pre- or post-natal development have been observed in animal reproduction studies at the highest doses of velpatasvir tested. In the mouse, rat, and rabbit embryo fetal studies, and rat pre/post-natal study velpatasvir exposure was approximately 31-fold, 6-fold, 0.7-fold, and 5-fold the exposure in humans at the recommended clinical dose, respectively.

Use with Ribavirin

If EPCLUSA is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for 6 months after the treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Refer to the ribavirin Product Monograph for a full list of warnings and precautions for ribavirin.

Nursing Women

It is not known whether sofosbuvir, velpatasvir, or their metabolites are excreted in human breast milk. The sofosbuvir predominant circulating metabolite GS-331007, and velpatasvir, are present in the milk of lactating rats; they had no clear effect on nursing pups. Because a risk to the newborn/infant cannot be excluded, mothers should be instructed not to breastfeed if they are taking EPCLUSA.

Pediatrics (< 18 years of age)

The safety and efficacy of EPCLUSA in pediatric patients have not been established.

Geriatrics (≥ 65 years of age)

The response rates observed for patients 65 years of age and over were similar to those of patients < 65 years of age across treatment groups.

Liver Transplant Patients

The safety and efficacy of EPCLUSA has not been established in patients with recurrent HCV infection after liver transplant.

HCV/HIV Co-infection

The safety and efficacy of EPCLUSA has not been established in HCV patients co-infected with Human Immunodeficiency Virus (HIV).

EPCLUSA has been shown to increase tenofovir exposure when used together with an HIV regimen containing tenofovir disoproxil fumarate (tenofovir DF). Patients receiving EPCLUSA concomitantly with tenofovir DF, particularly those at increased risk for renal dysfunction, should be monitored for tenofovir-associated adverse reactions. Refer to Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Efavirenz has been shown to significantly decrease the concentration of velpatasvir; therefore co-administration of EPCLUSA with an efavirenz-containing regimen is not recommended (see **DRUG INTERACTIONS**).

HCV/HBV Co-infection

EPCLUSA is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of EPCLUSA have not been established in HCV patients co-infected with HBV.

Monitoring and Laboratory Tests

If EPCLUSA is administered with amiodarone, close monitoring for bradycardia is recommended. Refer to the amiodarone Product Monograph (see **WARNINGS AND PRECAUTIONS**, **Drug Interactions**).

Monitoring of liver function including direct bilirubin is recommended in patients with decompensated cirrhosis (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The overall safety profile of EPCLUSA was established in non-cirrhotic and cirrhotic (compensated and decompensated) patients infected with HCV.

The safety assessment of EPCLUSA was based on pooled Phase 3 clinical trial data (ASTRAL-1, ASTRAL-2, and ASTRAL-3) from patients with HCV without cirrhosis or with compensated cirrhosis including 1035 patients who received EPCLUSA for 12 weeks. The proportion of patients who permanently discontinued treatment due to adverse events was 0.2% for patients receiving EPCLUSA for 12 weeks. Of the 1035 patients, 2% had at least one serious adverse

event (SAE), with no patients experiencing a treatment-related SAE.

The safety of EPCLUSA was also assessed in patients with decompensated cirrhosis (Child-Pugh B) in one Phase 3 trial (ASTRAL-4). In ASTRAL-4, the proportion of patients who permanently discontinued treatment due to adverse events was 5% (4/87) for those patients treated with EPCLUSA + RBV for 12 weeks, 1% (1/90) for those patients treated with EPCLUSA for 12 weeks, and 4% (4/90) for those patients treated with EPCLUSA for 24 weeks. Serious adverse events occurred in 19% (17/90), 16% (14/87) and 18% (16/90) of patients treated with EPCLUSA for 12 weeks, EPCLUSA + RBV for 12 weeks and EPCLUSA for 24 weeks, respectively. One patient (0.4%) experienced SAEs considered related to EPCLUSA.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Patients with Compensated Liver Disease:

The adverse reactions (Grades 2 to 4) observed in ≥ 2% of patients receiving 12 weeks of treatment with EPCLUSA in clinical trials are listed in Table 1.

Table 1. Adverse Reactions (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 Weeks of EPCLUSA[a] from the Pooled Phase 3 Studies (ASTRAL-1, ASTRAL-2, ASTRAL-3)

	EPCLUSA 12 weeks	Placebo 12 weeks
	N = 1035	N = 116
Headache	4%	3%
Fatigue	3%	1%

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Adverse reactions (Grades 2 to 4) occurring in less than 2% of patients receiving 12 weeks of treatment with EPCLUSA in clinical trials are listed below by body system:

Table 2. Adverse Reactions (Grades 2-4) Reported in < 2% of Patients Receiving 12 Weeks of EPCLUSA[a] from the Pooled Phase 3 Studies (ASTRAL-1, ASTRAL-2, ASTRAL-3)

Body System	EPCLUSA 12 Weeks
Blood And Lymphatic System Disorders	Leukopenia
Cardiac Disorders	Palpitations
Ear and labyrinth disorders	Vertigo
Gastrointestinal Disorders	Abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastroesophageal reflux disease, nausea, stomatitis, tongue coated, toothache, vomiting
General Disorders And Administration Site Conditions	Asthenia, chest pain, edema peripheral, influenza like illness, pain, pyrexia
Infections And Infestations	Lower respiratory tract infection, nasopharyngitis, sinusitis
Investigations	Electrocardiogram QT prolonged, weight decreased
Metabolism and Nutrition Disorders	Decreased appetite, gout, increased appetite
Musculoskeletal and Connective Tissue Disorders	Arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, neck pain, osteoarthritis, pain in extremity, spinal pain, tendon pain
Nervous System Disorders	Disturbance in attention, dizziness, dysgeusia, migraine, psychomotor hyperactivity, somnolence
Psychiatric Disorders	Anxiety, apathy, attention deficit/hyperactivity disorder, confusional state, depressed mood, depression, insomnia, irritability, loss of libido, mood swings, sleep disorder
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnoea, epistaxis, oropharyngeal pain
Skin And Subcutaneous Tissue Disorders	Alopecia, eczema, pruritus, pruritus generalised, rash, rash pruritic
Vascular Disorders	Hypertension, hypertensive crisis, hypotension

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Abnormal Hematologic and Clinical Chemistry Findings

The frequency of treatment-emergent laboratory abnormalities (Grades 2-4) occurring in at least 2% of patients receiving 12 weeks of treatment with EPCLUSA are described in Table 3.

Table 3. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 Weeks of EPCLUSA from the Pooled Phase 3 Studies (ASTRAL-1, ASTRAL-2, ASTRAL-3)

Laboratory Abnormality Parameters	EPCLUSA 12 weeks N = 1035	Placebo 12 weeks N = 116
Chemistry		
Hyperglycemia (> 8.91 mmol/L)	11%	12%
Hypoglycemia (< 3.03 mmol/L)	2%	< 1%
Lipase (> 1.5 x ULN)	8%	4%
Hematology		
Platelets (< 100 x 10^9/L)	2%	4%

ULN = Upper Limit of Normal

Patients With Decompensated Cirrhosis:

The adverse reactions (Grades 2 to 4) observed in ≥ 2% of patients receiving 12 or 24 weeks of treatment with EPCLUSA or 12 weeks of treatment with EPCLUSA plus ribavirin in the ASTRAL-4 study are listed in Table 4.

Table 4. Adverse Reactions (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 or 24 Weeks of EPCLUSA[a] without Ribavirin or 12 Weeks of EPCLUSA with Ribavirin in ASTRAL-4

	EPCLUSA 12 weeks N = 90	EPCLUSA + RBV 12 weeks N = 87	EPCLUSA 24 weeks N = 90
Anemia	0	14%	0
Decreased appetite	0	0	3%
Diarrhea	0	2%	0
Dyspnea	0	3%	0
Fatigue	2%	8%	3%
Headache	7%	1%	1%
Insomnia	0	2%	1%
Rash	1%	2%	0

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Adverse reactions (Grades 2 to 4) occurring in less than 2% of patients receiving 12 or 24 weeks of EPCLUSA or 12 weeks of EPCLUSA with ribavirin in ASTRAL-4 are listed below by body system:

Table 5. Adverse Reactions (Grades 2-4) Reported in < 2% of Patients Receiving 12 or 24 Weeks of EPCLUSA[a] or 12 Weeks of EPCLUSA with Ribavirin from ASTRAL-4

Body System	EPCLUSA 12 Weeks	EPCLUSA + RBV 12 Weeks	EPCLUSA 24 Weeks
Cardiac Disorders	N/A	Palpitations	N/A
Gastrointestinal Disorders	Vomiting	Vomiting	Abdominal discomfort, abdominal pain upper, gastroesophageal reflux disease
General Disorders And Administration Site Conditions	N/A	Asthenia	N/A
Hepatobiliary Disorders	N/A	N/A	Hepatorenal syndrome
Infections And Infestations	N/A	N/A	Peritonitis, sepsis
Investigations	N/A	N/A	Weight decreased
Metabolism and Nutrition Disorders	N/A	N/A	Diabetes mellitus
Musculoskeletal and Connective Tissue Disorders	Arthralgia	N/A	N/A
Nervous System Disorders	N/A	Headache, tremor	Headache, poor quality sleep
Psychiatric Disorders	Anxiety, depression	N/A	Anxiety, insomnia
Respiratory, Thoracic and Mediastinal Disorders	N/A	Dyspnea exertional	N/A
Skin And Subcutaneous Tissue Disorders	Rash	Pruritus, rash pruritic	Dermatitis contact
Vascular Disorders	N/A	Hypertension	Hypotension

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

N/A: Not applicable

Abnormal Hematologic and Clinical Chemistry Findings

The frequency of treatment-emergent laboratory abnormalities (Grades 2-4) occurring in at least 2% of patients receiving 12 or 24 weeks of treatment with EPCLUSA or 12 weeks of treatment with EPCLUSA + RBV are described in Table 6 below

Table 6. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Patients Receiving 12 or 24 Weeks of EPCLUSA or 12 Weeks of EPCLUSA with Ribavirin from ASTRAL-4

Laboratory Abnormality Parameters	EPCLUSA 12 Weeks	EPCLUSA + RBV 12 Weeks	EPCLUSA 24 Weeks
	N = 90	N = 87	N = 90
Chemistry			
Albumin (< 30 g/L)	14%	13%	17%
Alkaline phosphatase (> 2.5 x ULN)	2%	1%	0
Amylase (> 1.5 x ULN)	4%	6%	10%
AST (> 2.5 x ULN)	2%	1%	4%
Creatine kinase (≥ 6 x ULN)	4%	2%	3%
GGT (> 2.5 x ULN)	3%	0	3%
Hyperbilirubinemia (> 1.5 x ULN)	18%	54%	13%
Hyperglycemia (> 8.91 mmol/L)	42%	47%	47%
Hypokalemia (< 3.0 mmol/L)	2%	2%	1%
Hypoglycemia (< 3.03 mmol/L)	3%	0	7%
Hyponatremia (< 130 mmol/L)	8%	8%	9%
Lipase (> 1.5 x ULN)	29%	29%	30%
Hematology			
Hemoglobin (< 100 g/L)	9%	24%	11%
INR (> 1.5 x ULN)	1%	0	2%
Lymphocytes (< 0.6 x 10^9/L)	20%	38%	23%
Neutrophils (< 1.0 x 10^9/L)	3%	5%	9%
Platelets (< 100 x 10^9/L)	27%	31%	37%
White Blood Cells (< 2.0 x 10^9/L)	4%	13%	7%

ULN = Upper Limit of Normal

Among patients with decompensated cirrhosis in the ASTRAL-4 trial, direct bilirubin was found to remain stable (< 17.1 µmol/L change from baseline throughout treatment) in the majority of patients. One patient randomized to receive 24 weeks of treatment with EPCLUSA had a > 17.1 µmol/L increase from baseline in direct bilirubin from Week 6 through Week 10 for which no clinical explanation could be identified; this patient completed 24 weeks of treatment.

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, 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 when amiodarone is coadministered with sofosbuvir in combination with another HCV direct acting antiviral (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **DRUG INTERACTIONS**).

DRUG INTERACTIONS

Overview

As EPCLUSA contains sofosbuvir and velpatasvir, any interactions that have been identified with these agents individually may occur with EPCLUSA.

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

Drug-Drug Interactions

Potential for EPCLUSA to Affect Other Drugs

Velpatasvir is an inhibitor of drug transporter P-gp, breast cancer resistance protein (BCRP), OATP1B1 and OATP1B3. Coadministration of EPCLUSA with drugs that are substrates of these transporters may increase the exposure of such drugs. The drug-drug interaction potential of velpatasvir is limited to the presystemic processes (intestinal efflux and hepatic uptake); clinically relevant interactions in systemic circulation are not expected.

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 relevant inhibitors of efflux drug transporters P-gp, BCRP, renal efflux transporter MRP2, hepatic efflux transporter BSEP, hepatic uptake transporters OATP1B1, OATP1B3, OCT1, and GS-331007 is not an inhibitor of renal uptake transporters OAT1, OCT2 and renal efflux transporter MATE1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect EPCLUSA

Sofosbuvir and velpatasvir are substrates of efflux drug transporters P-gp and BCRP while GS-331007 is not. GS-331007 is not a substrate for renal transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2. Velpatasvir is poorly transported by OATP1B1 and OATP1B3. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

Drugs that are P-gp inducers and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. rifampin, St. John's wort or carbamazepine) may significantly 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**).

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. EPCLUSA may be coadministered with P-gp, BCRP, and CYP inhibitors.

Table 7 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. The table is not all-inclusive (see **ACTION AND CLINICAL PHARMACOLOGY**).

Table 7. Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
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)		It is recommended to 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 staggered from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g. omeprazole)		Proton-pump inhibitor doses comparable with omeprazole 20 mg or lower can be administered with EPCLUSA when EPCLUSA is administered with food.
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, Cardiovascular** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
digoxin[c]	↑ digoxin	Coadministration of EPCLUSA with digoxin may increase the concentration of digoxin due to intestinal inhibition of P-gp by velpatasvir. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with EPCLUSA.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Coadministration of EPCLUSA with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of EPCLUSA. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c] rifapentine*	↓ sofosbuvir ↓ velpatasvir	Coadministration of EPCLUSA with rifabutin, rifampin, or rifapentine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of EPCLUSA. Coadministration is not recommended.
Antiretrovirals: efavirenz[c]	↓ velpatasvir	Coadministration of EPCLUSA with efavirenz is expected to decrease the concentration of velpatasvir. Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Regimens containing tenofovir disoproxil fumarate[c] (tenofovir DF)	↑ tenofovir	EPCLUSA has been shown to increase tenofovir exposure. Patients receiving tenofovir DF and EPCLUSA concomitantly should be monitored for adverse reactions associated with tenofovir DF. Refer to the Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.
HMG-CoA Reductase Inhibitors rosuvastatin[c]	↑ rosuvastatin	Coadministration of EPCLUSA with rosuvastatin may 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.

*Drug not marketed in Canada

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

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 either observed or are expected when EPCLUSA is used with the following drugs: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, ketoconazole, lopinavir/ritonavir, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, or tacrolimus (see **DRUG INTERACTIONS**, **Assessment of Drug Interactions**).

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of sofosbuvir, GS-331007 and velpatasvir are shown in Table 8. The effects of sofosbuvir, velpatasvir or EPCLUSA on the exposure of coadministered drugs are shown in Table 9.

Table 8. Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007, and Velpatasvir in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofos-buvir Dose (mg)	Velpa-tasvir 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}
Antibiotic								
Rifampin[f]	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
Anti-HIV Drugs								
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)
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)
Dolutegravir	50 once daily	400 once daily	100 once daily	24	sofosbuvir	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
					GS-331007	1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
					velpatasvir	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)
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)

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	Velpatasvir 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}
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)
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)
Emtricitabine/ rilpivirine/ tenofovir DF[e]	200/25/300 once daily	400 once daily	100 once daily	24	sofosbuvir	1.09 (0.95, 1.25)	1.16 (1.09, 1.24)	NA
					GS-331007	0.96 (0.90, 1.01)	1.04 (1.00, 1.07)	1.12 (1.07, 1.17)
					velpatasvir	0.96 (0.85, 1.10)	0.99 (0.88, 1.11)	1.02 (0.91, 1.15)
Lopinavir/ ritonavir + emtricitabine/ tenofovir DF	4 x 200/50 + 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)
Raltegravir + emtricitabine/ tenofovir DF	400 twice daily+200/300 once daily	400 once daily	100 once daily	30	sofosbuvir	1.09 (0.97, 1.23)	1.16 (1.07, 1.25)	NA
					GS-331007	0.95 (0.91, 0.98)	1.03 (1.00, 1.06)	1.08 (1.04, 1.13)
					velpatasvir	0.97 (0.87, 1.08)	0.98 (0.88, 1.10)	0.97 (0.87, 1.07)
Azole Anti-fungal								
Ketoconazole[f]	200 twice daily	ND	100 single dose	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	Velpatasvir 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}
H2-Receptor Antagonists								
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
Immunosuppressants								
Cyclosporine[f]	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
Tacrolimus[f]	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
Opiate Agonist								
Methadone[f]	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

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	Velpatasvir 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}
Proton Pump Inhibitors								
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	100 single dose fed	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 EPCLUSA	400 single dose fed	100 single dose fed	38	sofosbuvir	0.79 (0.68, 0.92)	1.05 (0.94, 1.16)	NA
					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	100 single dose fed	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

NA = not available/not applicable, ND = not dosed.

a All interaction studies conducted in healthy volunteers.

b Administered as ATRIPLA® (efavirenz/emtricitabine/tenofovir DF fixed-dose combination).

c Administered as GENVOYA® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose single tablet regimen).

d Administered as STRIBILD® (elvitegravir/cobicistat/emtricitabine/tenofovir DF fixed-dose single tablet regimen).

e Administered as COMPLERA® (emtricitabine/rilpivirine/tenofovir DF fixed-dose combination).

f These studies have not been performed with EPCLUSA; they were conducted with either sofosbuvir or velpatasvir administered as single agents.

Table 9. 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)	Sofos-buvir dose (mg)	Velpa-tasvir 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}
Anti-HIV							
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 once daily				1.01 (0.96, 1.06)	1.02 (0.99, 1.04)	1.06 (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)
Dolutegravir	50 once daily	400 once daily	100 once daily	24	1.06 (1.01, 1.11)	1.06 (1.01, 1.13)	1.04 (0.98, 1.10)
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

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofos-buvir dose (mg)	Velpa-tasvir 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}
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)
Lopinavir/ritonavir + emtricitabine/ tenofovir DF	Lopinavir 200 x 4 once daily	400 once daily	100 once daily	24	0.97 (0.92, 1.02)	1.00 (0.93, 1.06)	1.11 (0.96, 1.30)
	Ritonavir 50 x 4 once daily				0.94 (0.83, 1.07)	0.97 (0.89, 1.05)	1.07 (0.95, 1.20)
	Emtricitabine 200 once daily				1.02 (0.93, 1.12)	1.00 (0.94, 1.06)	0.97 (0.91, 1.04)
	Tenofovir DF 300 once daily				1.42 (1.27, 1.57)	1.22 (1.14, 1.31)	1.28 (1.20, 1.37)
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)
Cardiac Glycoside							
Digoxin	0.25 single dose	ND	100 once daily	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA
Estrogen-based Contraceptives							
Norelgestromin[h]	Norgestimate 0.180/0.215/ 0.250/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)

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofos-buvir dose (mg)	Velpa-tasvir 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}
Norgestrel[h]		ND	100 once daily	13	0.96 (0.78, 1.19)	0.91 (0.73, 1.15)	0.92 (0.73, 1.18)
		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[h]		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)
Immunosuppressants							
Cyclosporine[h]	600 single dose	400 single dose	ND	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
		ND	100 single dose	12	0.92 (0.82, 1.02)	0.88 (0.78, 1.00)	NA
Tacrolimus[h]	5 single dose	400 single dose	ND	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Opiate Agonists							
R-Methadone[h]	30 to 130 daily	400 once daily	ND	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone[h]					0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)
Statins							
Pravastatin[h]	40 single dose	ND	100 once daily	18	1.28 (1.08, 1.52)	1.35 (1.18, 1.54)	NA
Rosuvastatin[h]	10 single dose	ND	100 once daily	18	2.61 (2.32, 2.92)	2.69 (2.46, 2.94)	NA

NA = not available/not applicable, ND = not dosed.

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 single tablet regimen).

f Administered as STRIBILD (elvitegravir, cobicistat, emtricitabine and tenofovir DF fixed-dose single tablet regimen).

g Administered as COMPLERA (emtricitabine, rilpivirine and tenofovir DF fixed-dose combination).

h These studies have not been performed with EPCLUSA; they were conducted with either sofosbuvir or velpatasvir administered as single agents.

Drug-Food Interactions

No interactions between EPCLUSA and food have been identified.

Drug-Herb Interactions

St. John's wort should not be used with EPCLUSA.

Coadministration of St. John's wort, a potent P-gp and CYP inducer, may decrease sofosbuvir and velpatasvir plasma concentrations, which may result in loss of therapeutic effect. See **WARNINGS AND PRECAUTIONS**, **General, Use with Potent P-gp Inducers and/or Potent or Moderate CYP Inducers**.

Drug-Laboratory Interactions

Interactions of EPCLUSA with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

EPCLUSA is a single tablet regimen. No dosage adjustments are possible for EPCLUSA.

The recommended dose of EPCLUSA is one tablet of 400 mg/100 mg sofosbuvir/velpatasvir, taken orally, once daily with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, *Effects of Food***).

The recommended dose and treatment duration for EPCLUSA is provided in Table 10.

Table 10. Recommended Treatment Regimen (All HCV Genotypes)

Patient Population	Recommended Dose and Duration of Treatment
Patients without cirrhosis and patients with compensated cirrhosis	EPCLUSA one tablet daily for 12 weeks
Patients with decompensated cirrhosis[a]	EPCLUSA one tablet daily + ribavirin[b] for 12 weeks

a Limited data for genotypes 2, 4, 5 and 6 (see **WARNINGS AND PRECAUTIONS**, and **CLINICAL TRIALS**)

b When administered with EPCLUSA, the recommended dose of ribavirin is based on weight: 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 with food. For ribavirin dose modifications, refer to the Product Monograph containing ribavirin information.

Special Populations

Pediatrics (< 18 Years of age)

EPCLUSA is not indicated for use in pediatric patients < 18 years of age.

Geriatrics (≥ 65 years of age)

No dose adjustment is warranted for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic Impairment

No dose adjustment of EPCLUSA is required for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). Based on pharmacokinetic data, no dose adjustment of EPCLUSA is required for patients with Child-Pugh Class C hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**). However, safety and efficacy of EPCLUSA have not been established in patients with Child-Pugh Class C decompensated cirrhosis.

Renal Impairment

No dose adjustment of EPCLUSA is required for patients with mild or moderate renal impairment. The safety and efficacy of EPCLUSA has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or ESRD requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY**).

Missed Dose

If a patient misses a dose of EPCLUSA within 18 hours of the time it is usually taken, the patient should take EPCLUSA as soon as possible, and then take the next dose of EPCLUSA at the regularly scheduled time.

If a patient misses a dose of EPCLUSA and it is after 18 hours of the time it is usually taken, the patient should not take the missed dose, but resume the usual dosing schedule. A double dose of EPCLUSA must not be taken.

If a patient vomits less than 3 hours after taking a dose of EPCLUSA, the patient should take another dose of EPCLUSA. If a patient vomits more than 3 hours after taking a dose of EPCLUSA, the patient should take the next dose at the regularly scheduled time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Administration of activated charcoal may be used to aid in the removal of unabsorbed active substance. General supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient are recommended.

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.

The highest documented doses of sofosbuvir and velpatasvir were a single dose of 1200 mg and a single dose of 500 mg, respectively. In these healthy volunteer studies, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

ACTION AND CLINICAL PHARMACOLOGY

Description

EPCLUSA is a fixed-dose single tablet regimen of sofosbuvir and velpatasvir.

Sofosbuvir is a nucleotide analog pan-genotypic NS5B polymerase inhibitor. Velpatasvir is a pan-genotypic HCV NS5A inhibitor.

Mechanism of Action

EPCLUSA

Both sofosbuvir and velpatasvir exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV NS5B and NS5A proteins respectively. Both compounds display low cytotoxicity in a number of distinct cell lines and display no significant antiviral activity against other viruses tested. *In vitro* combination studies using both sofosbuvir and velpatasvir showed an additive effect as measured by *in vitro* cell based HCV replicon assays, with no antagonism detected. As individual components, both sofosbuvir and velpatasvir showed additive to synergistic activity with all other anti-HCV agents.

Sofosbuvir

Sofosbuvir is a pan-genotypic polymerase inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203).

Velpatasvir

Velpatasvir is a pan-genotypic HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. *In vitro* resistance selection and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Pharmacodynamics

Effect on Electrocardiogram

The effects of administration of supratherapeutic doses of sofosbuvir (1200 mg) and velpatasvir (500 mg) (as individual drugs) demonstrated a lack of effect of sofosbuvir or velpatasvir on QTc interval.

Pharmacokinetics

Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg. 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, indicating velpatasvir absorption is solubility limited.

The pharmacokinetics of EPCLUSA are shown in Table 11.

Table 11. Summary of Pharmacokinetics for Once-Daily Administration of EPCLUSA in Healthy Adult Subjects and HCV-Infected Patients

PK Parameters	Healthy Subjects[a] EPCLUSA N = 331 Geometric Mean (Range)			HCV-Infected Patients[b] EPCLUSA N = 1428 Geometric Mean (Range)		
	SOF	GS-331007	VEL	SOF[c]	GS-331007	VEL[d]
AUC_{0-24} (ng·h/mL)	1272 (543, 2348)	12040 (6983, 20488)	4556 (612, 12185)	1262 (337, 5333)	13967 (5217, 44182)	2967 (603, 11503)
C_{max} (ng/mL)	550 (187, 1171)	817 (453, 1448)	421 (47, 1066)	566 (143, 1582)	868 (284, 2113)	259 (39, 977)
C_{min} (ng/mL)	ND	ND	65 (9, 243)	ND	ND	41 (5, 236)

ND = not determined; SOF = sofosbuvir; VEL = velpatasvir
a. Population PK analysis from Phase 1 studies.
b. Population PK analysis from Phase 2 and 3 studies.
c. N=982; 446 patients did not have estimable PK parameters for SOF
d. N=1425; 3 patients did not have estimable PK parameters for VEL

Based on population PK analyses, sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection. Relative to healthy subjects (N=331), velpatasvir AUC_{0-24} and C_{max} were 37% lower and 41% lower, respectively, in HCV-infected patients. Age, race, BMI, HCV genotype or the presence or absence of cirrhosis had no clinically relevant effects on the exposure of sofosbuvir, GS-331007, or velpatasvir.

Absorption

Following oral administration of EPCLUSA, sofosbuvir median peak plasma concentration was observed 0.5-1.0 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.0 hours post-dose. Velpatasvir median peak concentrations were observed 3.0 hours post-dose.

Effects of Food

Relative to fasting conditions, the administration (to healthy subjects) of a single dose of EPCLUSA with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal delayed the absorption of both sofosbuvir (median t_{max} delayed from 0.5 hours to 2.0 hours) and velpatasvir (median t_{max} delayed from 3.0 hours to 4.0 hours).

The extent of sofosbuvir absorption was significantly higher when administered with food (AUC increased 60% and 78% with a moderate fat or a high fat meal, respectively) and the C_{max} was unchanged. Food did not alter GS-331007 AUC but resulted in a 25% and 37% decrease in C_{max}, when EPCLUSA was administered with a moderate fat or a high fat meal, respectively.

The extent of velpatasvir absorption was increased more with a moderate fat meal (AUC increased 35% and C_{max} increased 31%) than with a high fat meal (AUC increased by 22% and no significant change in C_{max}).

The response rates in Phase 3 trials were similar in HCV-infected patients who received EPCLUSA with food or without food. EPCLUSA can be administered without regard to food.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Velpatasvir is > 99.5% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 μg/mL to 1.8 μg/mL. After a single 100 mg dose of [^{14}C]-velpatasvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.52 and 0.67.

Metabolism

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate, GS-461203. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for greater than 90% of total systemic exposure.

In vitro, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed. Following a single dose of 100 mg [^{14}C]-velpatasvir to healthy human male subjects, the majority (> 98%) of radioactivity in plasma was the parent drug. Unchanged velpatasvir is the major species present in feces.

Excretion

Sofosbuvir is primarily eliminated in the urine as GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of EPCLUSA were 0.5 and 25 hours, respectively.

Biliary excretion of parent drug was the major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of EPCLUSA was approximately 15 hours.

Special Populations and Conditions

Pediatrics (< 18 years of age)

The pharmacokinetics of sofosbuvir, GS-331007 and velpatasvir in pediatric patients have not been established.

Geriatrics (≥ 65 years of age)

Based on population pharmacokinetic analyses, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007 or velpatasvir. Clinical studies of EPCLUSA included 156 patients aged 65 and over. The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

Gender

No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir, GS-331007, or velpatasvir.

Race

No clinically relevant pharmacokinetic differences due to race have been identified for sofosbuvir, GS-331007, or velpatasvir.

Hepatic Insufficiency

Hepatic impairment studies were conducted with the individual drugs, sofosbuvir and velpatasvir.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Mild hepatic impairment is not expected to meaningfully alter the pharmacokinetics of sofosbuvir and GS-331007. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

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 patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of velpatasvir.

Renal Insufficiency

Renal impairment studies have been conducted with the individual drugs, sofosbuvir and velpatasvir.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR $\geq$ 50 and < 80 mL/min/1.73m^2), moderate (eGFR $\geq$ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir (N=6/group). Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD, sofosbuvir AUC_{inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The AUC_{inf} of GS-331007 in subjects with ESRD administered sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects.

Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. Following a single 400 mg dose of sofosbuvir, a 4 hour hemodialysis session removed approximately 18% of administered dose.

Velpatasvir is primarily excreted in feces. Exposure of velpatasvir is not significantly impacted in the setting of severe renal impairment. The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Velpatasvir AUC and C_{max} were approximately 50%

and 11% higher, respectively, in subjects with severe renal impairment compared to control subjects with normal renal function; these differences are not considered clinically relevant.

STORAGE AND STABILITY

Store below 30 °C (86 °F).

- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EPCLUSA is a single tablet regimen containing sofosbuvir and velpatasvir for oral administration.

Each tablet contains 400 mg of sofosbuvir and 100 mg of 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.

EPCLUSA is available as a pink colored, diamond shaped, film-coated tablet debossed with “GSI” on one side and “7916” on the other side of the tablet. Each bottle contains 28 tablets, a polyester coil and closed with a child resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

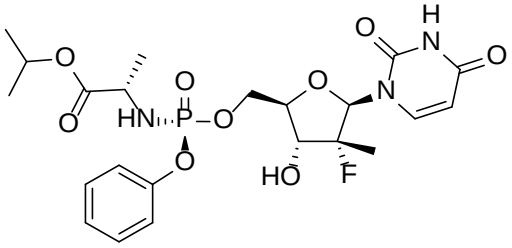
Proper name: **sofosbuvir**

Chemical name: (*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

Molecular formula: $C_{22}H_{29}FN_3O_9P$

Molecular mass: 529.45

Structural formula:



Physicochemical properties:

Appearance: Sofosbuvir is a white to off-white crystalline solid.

Solubility: Sofosbuvir is slightly soluble in water.

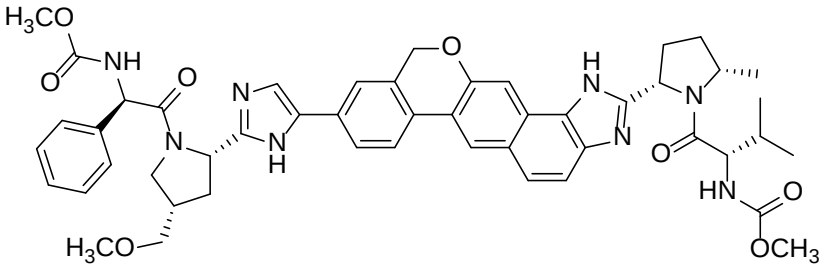
Proper name: **velpatasvir**

Chemical name: 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-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Molecular formula: $C_{49}H_{54}N_8O_8$

Molecular mass: 883.00

Structural formula:



Physicochemical properties:

Appearance	Velpatasvir is a white to tan or yellow solid.
Solubility	Velpatasvir is practically insoluble (< 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2.0, and soluble (> 36 mg/mL) at pH 1.2.

CLINICAL TRIALS

The efficacy of EPCLUSA was evaluated in three Phase 3 trials with data available for a total of 1035 patients with genotype 1 to 6 chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis. The efficacy of EPCLUSA was also evaluated in one Phase 3 trial in 267 patients with HCV infection with decompensated cirrhosis (ASTRAL-4).

Sustained virologic response (SVR), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint to determine the HCV cure rate.

The demographics and baseline characteristics for the patients in studies ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4 were balanced across the treatment groups for each study and are summarized in Table 13, Table 17, Table 21, and Table 25, respectively.

The ribavirin (RBV) dose was weight-based (1,000 mg daily administered in two divided doses for patients < 75 kg and 1,200 mg for those ≥ 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. RBV dose adjustments were performed according to the Product Monograph for RBV. 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 per mL.

Clinical Trials in Patients with Compensated Liver Disease

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

Trial Design

Table 12. Summary of Trial Design in Genotypes 1, 2, 4, 5, 6 HCV Patients with or without Cirrhosis (ASTRAL-1)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, double-blind, placebo-controlled, multicentre	EPCLUSA (400 mg/100 mg), QD, PO or Placebo, QD, PO	EPCLUSA	12 weeks
		Placebo	12 weeks

PO = orally; QD = once a day

Patients with genotype 1, 2, 4, or 6 HCV were randomized in a 5:1 ratio to treatment with EPCLUSA for 12 weeks or placebo for 12 weeks. Patients with genotype 5 HCV were enrolled to the EPCLUSA group. Randomization was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of cirrhosis.

Demographics and Other Baseline Characteristics

Table 13. Demographic and Other Baseline Characteristics of Genotypes 1, 2, 4, 5, 6 HCV Patients with or without Cirrhosis (ASTRAL-1)

Characteristics	EPCLUSA 12 Weeks N = 624	Placebo 12 Weeks N = 116
Age (years)		
Mean (range)	54 (18-82)	53 (25-74)
Gender, n (%)		
Male	374 (60)	68 (59)
Female	250 (40)	48 (41)
Race, n (%*)		
White	493 (79)	90 (78)
Black	52 (8)	11 (9)
Asian	62 (10)	11 (9)
Other	14 (2)	4 (3)
Not disclosed	3 (< 1)	0
BMI, n (%)		
< 30 kg/m^2	489 (78)	93 (80)
≥ 30 kg/m^2	135 (22)	23 (20)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.3 ± 0.7	6.3 ± 0.6
< 800,000 copies/mL, n (%)	163 (26)	29 (25)
≥ 800,000 copies/mL, n (%)	461 (74)	87 (75)

Characteristics	EPCLUSA 12 Weeks N = 624	Placebo 12 Weeks N = 116
HCV genotype, n (%*)		
1	328 (53)	65 (56)
1a	210 (34)	46 (40)
1b	118 (19)	19 (16)
2	104 (17)	21 (18)
4	116 (19)	22 (19)
5	35 (6)	0
6	41 (7)	8 (7)
IL28B, n (%*)		
CC	186 (30)	36 (31)
Non-CC	433 (69)	79 (68)
Missing	5 (< 1)	1 (< 1)
Cirrhosis, n (%*)		
Yes (compensated)	121 (19)	21 (18)
No	501 (80)	95 (82)
Missing	2 (< 1)	0
Treatment Status, n (%)		
Treatment-naïve	423 (68)	83 (72)
Treatment experienced	201 (32)	33 (28)
Prior HCV Treatment, n (%)		
DAA+Peg-IFN+RBV	56/201 (28)	6/33 (18)
Peg-IFN+RBV	122/201 (61)	24/33 (73)
Other	23/201 (11)	3/33 (9)
Prior HCV Response, n (%*)		
Nonresponder	96/201 (48)	14/33 (42)
Relapse/Breakthrough	103/201 (51)	19/33 (58)
Not applicable	2/201 (< 1)	0/33

DAA = direct acting antiviral; Peg-IFN = pegylated interferon; RBV= ribavirin; SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the EPCLUSA treatment group by HCV genotypes in the ASTRAL-1 trial are presented in Table 14. The EPCLUSA 12 Week group met the primary endpoint of an SVR12 rate that was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$). No patient in the EPCLUSA 12 Week group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse). No patient in the placebo group achieved SVR12.

Table 14. SVR12 and Virologic Failure in Genotypes 1, 2, 4, 5, 6 HCV Infected Patients with or without Cirrhosis (ASTRAL-1)

	EPCLUSA 12 weeks (N = 624)							
	Total (all GTs) (N=624) % (n/N)	**GT-1**			**GT-2 (N=104) % (n/N)**	**GT-4 (N=116) % (n/N)**	**GT-5 (N=35) % (n/N)**	**GT-6 (N=41) % (n/N)**
		GT-1a (N=210) % (n/N)	**GT-1b (N=118) % (n/N)**	**Total (N=328) % (n/N)**				
SVR12[a]	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 Patients without SVR								
Overall Virologic Failure	< 1 (2/624)	< 1 (1/210)	< 1 (1/118)	< 1 (2/328)	0/104	0/116	0/35	0/41
On-Treatment Virologic Failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse[b]	< 1 (2/623)	< 1 (1/209)	< 1 (1/118)	< 1 (2/327)	0/104	0/116	0/35	0/41
Other[c]	< 1 (4/624)	< 1 (3/210)	0/118	< 1 (3/328)	0/104	0/116	3 (1/35)	0/41

GT = genotype

a SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.

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

c Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 15.

Table 15. Sustained Virologic Response (SVR) for Select Subgroups of Genotypes 1, 2, 4, 5, 6 HCV Patients with or without Cirrhosis (ASTRAL-1)

	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)				
	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
Cirrhosis								
Yes (compensated)	99 (120/121)	100 (49/49)	96 (23/24)	99 (72/73)	100 (10/10)	100 (27/27)	100 (5/5)	100 (6/6)
No	99 (496/501)	98 (157/161)	100 (94/94)	98 (251/255)	100 (93/93)	100 (89/89)	97 (28/29)	100 (35/35)
Missing	100 (2/2)	0/0	0/0	0/0	100 (1/1)	0/0	100 (1/1)	0/0
Prior HCV Treatment Experience								
Treatment-naïve	99 (418/423)	97 (128/132)	100 (86/86)	98 (214/218)	100 (79/79)	100 (64/64)	96 (23/24)	100 (38/38)
Treatment experienced	> 99 (200/201)	100 (78/78)	97 (31/32)	99 (109/110)	100 (25/25)	100 (52/52)	100 (11/11)	100 (3/3)

GT = genotype

High SVR12 rates were achieved in all subgroups across all HCV genotypes. All patients previously treated with a direct acting antiviral (DAA) + Peg-IFN+RBV achieved SVR12 (56 of 56, 100%), which included 48, 6, and 2 patients with genotype 1, 4, and 5 HCV infection, respectively.

Genotype 2 HCV Infected Adults (ASTRAL-2)

Trial Design

Table 16. Summary of Trial Design in Genotype 2 HCV Patients with or without Cirrhosis (ASTRAL-2)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	EPCLUSA (400 mg/100 mg), QD, PO or SOF 400 mg QD + RBV 1000 or 1200 mg/day, BID, PO	EPCLUSA	12 weeks
		SOF+RBV	12 weeks

BID = twice a day; PO = orally; QD = once a day; RBV = ribavirin; SOF = sofosbuvir

Patients were randomized in a 1:1 ratio to treatment with EPCLUSA for 12 weeks or SOF+RBV for 12 weeks. Randomization was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve vs treatment experienced).

Demographic and Baseline Characteristics

Table 17. Demographic and Other Baseline Characteristics of Genotype 2 HCV Patients with or without Cirrhosis (ASTRAL-2)

Characteristics	EPCLUSA 12 Weeks N = 134	SOF+RBV 12 Weeks N = 132
Age (years)		
Mean (range)	57 (26–81)	57 (23-76)
Gender, n (%)		
Male	86 (64)	72 (55)
Female	48 (36)	60 (45)
Race, n (%*)		
White	124 (93)	111 (84)
Black	6 (4)	12 (9)
Asian	1 (< 1)	5 (4)
Other	1 (< 1)	3 (2)
Not disclosed	2 (1)	1 (< 1)
BMI, n (%)		
< 30 kg/m^2	95 (71)	84 (64)
≥ 30 kg/m^2	39 (29)	48 (36)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.5 ± 0.8	6.4 ± 0.7
< 800,000 copies/mL, n (%)	23 (17)	31 (23)
≥ 800,000 copies/mL, n (%)	111 (83)	101 (77)
HCV genotype, n (%)		
2	134 (100)	132 (100)
2 (no confirmed subtype)	13 (10)	12 (9)
2a	2 (1)	4 (3)
2a/2c	16 (12)	12 (9)
2b	103 (77)	104 (79)
IL28B, n (%)		
CC	55 (41)	46 (35)
Non-CC	79 (59)	86 (65)
Cirrhosis, n (%*)		
Yes (compensated)	19 (14)	19 (14)
No	115 (86)	112 (85)
Missing	0	1 (< 1)
Prior HCV Treatment Experience, n (%)		
Treatment-naïve	115 (86)	112 (85)
Treatment experienced	19 (14)	20 (15)
Prior HCV Treatment, n (%)		
Peg-IFN+RBV	16/19 (84)	15/20 (75)
Other	3/19 (16)	5/20 (25)

Characteristics	EPCLUSA 12 Weeks N = 134	SOF+RBV 12 Weeks N = 132
Prior HCV Response, n (%)		
Nonresponder	3/19 (16)	3/20 (15)
Relapse/Breakthrough	16/19 (84)	17/20 (85)

Peg-IFN = pegylated interferon; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the treatment groups in the ASTRAL-2 trial are presented in Table 18. Treatment with EPCLUSA for 12 weeks demonstrated statistical superiority (p = 0.018) compared to treatment with SOF+RBV for 12 weeks (treatment difference +5.2%; 95% confidence interval: +0.2% to +10.3%).

Table 18. SVR12 and Virologic Failure in Genotype 2 HCV Infected Patients with or without Cirrhosis (ASTRAL-2)

	EPCLUSA 12 Weeks N = 134 % (n/N)	SOF+RBV 12 Weeks N = 132 % (n/N)
SVR12[a]	99 (133/134)	94 (124/132)
Outcome for patients without SVR		
Overall Virologic Failure	0/134	5 (6/132)
On-Treatment Virologic Failure	0/134	0/132
Relapse[b]	0/133	5 (6/132)
Other[c]	< 1 (1/134)	2 (2/132)

RBV = ribavirin; SOF = sofosbuvir
a. SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ at 12 weeks (Lower Limit of Quantitation, 15 IU/mL) after the cessation of treatment.
b. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 19.

Table 19. Sustained Virologic Response (SVR) for Select Subgroups of Genotype 2 HCV Patients with or without Cirrhosis (ASTRAL-2)

Study Outcomes	EPCLUSA 12 Weeks N = 134 % (n/N)	SOF+RBV 12 Weeks N = 132 % (n/N)
Genotype[a]		
2 (no confirmed subtype)	100 (13/13)	92 (11/12)
2a	100 (2/2)	100 (4/4)
2a/2c	100 (16/16)	92 (11/12)
2b	99 (102/103)	94 (98/104)
Cirrhosis		
Yes (compensated)	100 (19/19)	95 (18/19)
No	99 (114/115)	94 (105/112)
Missing	0/0	100 (1/1)
Prior HCV Treatment Experience		
Treatment-naïve	99 (114/115)	96 (107/112)
Treatment experienced	100 (19/19)	85 (17/20)
Nonresponder	100 (3/3)	67 (2/3)
Relapse/Breakthrough	100 (16/16)	88 (15/17)

RBV = ribavirin; SOF = sofosbuvir

Genotype 3 HCV Infected Adults (ASTRAL-3)

Trial Design

Table 20. Summary of Trial Design in Genotype 3 HCV Patients with or without Cirrhosis (ASTRAL-3)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	EPCLUSA (400 mg/100 mg), QD, PO	EPCLUSA	12 weeks
	SOF 400 mg QD, PO + RBV 1000 or 1200 mg/day, BID, PO	SOF+RBV	24 weeks

BID = twice a day; PO = orally; QD = once a day; RBV = ribavirin; SOF = sofosbuvir

Patients were randomized in a 1:1 ratio to treatment with EPCLUSA for 12 weeks or SOF+RBV for 24 weeks. Randomization was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve vs treatment experienced).

Demographics and Other Baseline Characteristics

Table 21. Demographic and Other Baseline Characteristics of Genotype 3 HCV Patients with or without Cirrhosis (ASTRAL-3)

Characteristics	EPCLUSA 12 Weeks N = 277	SOF+RBV 24 Weeks N = 275
Age (years)		
Mean (range)	49 (21–76)	50 (19–74)
Gender, n (%)		
Male	170 (61)	174 (63)
Female	107 (39)	101 (37)
Race, n (%*)		
White	250 (90)	239 (87)
Black	3 (1)	1 (< 1)
Asian	23 (8)	29 (11)
Other	1 (< 1)	5 (2)
Not disclosed	0	1 (< 1)
BMI, n (%)		
< 30 kg/m^2	226 (82)	214 (78)
≥ 30 kg/m^2	51 (18)	61 (22)
Viral Load		
HCV RNA Log_{10} IU/mL, mean ± SD	6.2 ± 0.7	6.3 ± 0.7
< 800,000 copies/mL, n (%)	86 (31)	81 (29)
≥ 800,000 copies/mL, n (%)	191 (69)	194 (71)
HCV genotype, n (%*)		
3	277 (100)	275 (100)
3a	265 (96)	250 (91)
3b	2 (< 1)	5 (2)
3h	0	2 (< 1)
3k	1 (< 1)	0
3 (no confirmed subtype)	9 (3)	18 (7)
IL28B, n (%)		
CC	105 (38)	111 (40)
Non-CC	172 (62)	164 (60)
Cirrhosis, n (%)		
Yes (compensated)	80 (29)	83 (30)
No	197 (71)	187 (68)
Missing	0	5 (2)
Prior HCV Treatment Experience, n (%)		
Treatment-naïve	206/277 (74)	204/275 (74)
Treatment experienced	71/277 (26)	71/275 (26)
Prior HCV Treatment, n (%*)		
DAA+Peg-IFN+RBV	1/71 (1)	0/71
Peg-IFN+RBV	64/71 (90)	65/71 (92)
Other	6/71 (8)	6/71 (8)
Prior HCV Response, n (%)		
Nonresponder	20/71 (28)	24/71 (34)
Relapse/Breakthrough	51/71 (72)	47/71 (66)

DAA = direct acting antiviral; Peg-IFN = pegylated interferon; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir
*Total percentage may not add to 100% due to rounding.

Study Results

The response rates for the treatment groups in study ASTRAL-3 are presented in Table 22. Treatment with EPCLUSA for 12 weeks demonstrated statistical superiority ($p < 0.001$) compared to treatment with SOF+RBV for 24 weeks (treatment difference +14.8%; 95% confidence interval: +9.6% to +20.0%).

Table 22. SVR12 and Virologic Failure in Genotype 3 HCV Infected Patients with or with Cirrhosis (ASTRAL-3)

	EPCLUSA 12 Weeks N = 277 % (n/N)	**SOF+RBV 24 Weeks N = 275 % (n/N)**
SVR12[a]	95 (264/277)	80 (221/275)
Overall Virologic Failure	4 (11/277)	14 (39/275)
On-Treatment Virologic Failure	0/277	< 1 (1/275)
Relapse[b]	4 (11/276)	14 (38/272)
Other[c]	< 1 (2/277)	5 (15/275)

RBV = ribavirin; SOF = sofosbuvir

a. SVR12, Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 15 IU/mL) at 12 weeks after the cessation of treatment.
b. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Response rates for selected subgroups are presented in Table 23.

Table 23. Sustained Virologic Response (SVR) for Select Subgroups of Genotype 3 HCV Patients with or without Cirrhosis (ASTRAL-3)

Study Outcomes	**EPCLUSA 12 Weeks N = 277 % (n/N)**	**SOF +RBV 24 Weeks N = 275[a] % (n/N)**
Genotype		
3a	95 (253/265)	80 (199/250)
3b	100 (2/2)	100 (5/5)
3h	0	100 (2/2)
3k	100 (1/1)	0
3 (no confirmed subtype)	89 (8/9)	83 (15/18)
Cirrhosis by Prior HCV Treatment Experience		
Treatment-Naïve		
With Cirrhosis (compensated)	93 (40/43)	73 (33/45)
Without Cirrhosis	98 (160/163)	90 (141/156)
Missing	0/0	67 (2/3)
Treatment Experienced		
With Cirrhosis (compensated)	89 (33/37)	58 (22/38)
Without Cirrhosis	91 (31/34)	71 (22/31)

Study Outcomes	EPCLUSA 12 Weeks N = 277 % (n/N)	SOF +RBV 24 Weeks N = 275[a] % (n/N)
Missing	0/0	50 (1/2)
Response to Prior HCV Therapy		
Non-Responder	85 (17/20)	58 (14/24)
Relapse/Breakthrough	92 (47/51)	66 (31/47)
Prior HCV Therapy		
DAA+PEG-IFN+RBV	100 (1/1)	0
PEG-IFN+RBV	89 (57/64)	63 (41/65)
Other	100 (6/6)	67 (4/6)

DAA = direct acting antiviral; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

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

The overall SVR12 (virologic cure) across the three trials (ASTRAL-1, ASTRAL-2, ASTRAL-3) was 98% (1015/1035).

Clinical Trial in Patients with Decompensated Cirrhosis (ASTRAL-4)

Trial Design

Table 24. Summary of Trial Design in HCV Patients with Decompensated Cirrhosis (ASTRAL-4)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	EPCLUSA (400 mg/100 mg), QD, PO	EPCLUSA	12 weeks
	EPCLUSA (400 mg/100 mg), QD, PO + RBV 1000 or 1200 mg/day, BID, PO	EPCLUSA + RBV	12 weeks
	EPCLUSA (400 mg/100 mg), QD, PO	EPCLUSA	24 weeks

BID = twice a day; PO = orally; QD = once a day; RBV = ribavirin; SOF = sofosbuvir

Patients were randomized in a 1:1:1 ratio to treatment with EPCLUSA for 12 weeks, EPCLUSA + RBV for 12 weeks or EPCLUSA for 24 weeks. Randomization was stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate). No patients with genotype 5 HCV infection were enrolled.

Demographics and Other Baseline Characteristics

Table 25. Demographic and Other Baseline Characteristics of HCV Patients with Decompensated Cirrhosis (ASTRAL-4)

Characteristics	EPCLUSA 12 Weeks N = 90	EPCLUSA + RBV 12 Weeks N = 87	EPCLUSA 24 Weeks N = 90
Age (years)			
Mean (range)	58 (42–73)	58 (40-71)	58 (46-72)
Gender, n (%)			
Male	57 (63)	66 (76)	63 (70)
Female	33 (37)	21 (24)	27 (30)
Race, n (%)			
White	79 (88)	79 (91)	81 (90)
Black	6 (7)	5 (6)	6 (7)
Asian	3 (3)	0	2 (2)
Other	2 (2)	3 (3)	0
Not disclosed	0	0	1 (1)
BMI, n (%)			
< 30 kg/m^2	48 (53)	54 (62)	52 (58)
≥ 30 kg/m^2	42 (47)	33 (38)	38 (42)
Viral Load			
HCV RNA Log10 IU/mL, mean ± SD	6.0 ± 0.5	5.8 ± 0.6	5.9 ± 0.6
< 800,000 copies/mL, n (%)	31 (34)	42 (48)	45 (50)
≥ 800,000 copies/mL, n (%)	59 (66)	45 (52)	45 (50)
HCV genotype, n (%*)			
1	68 (76)	68 (78)	71 (79)
1a	50 (56)	54 (62)	55 (61)
1b	18 (20)	14 (16)	16 (18)
2	4 (4)	4 (5)	4 (4)
3	14 (16)	13 (15)	12 (13)
4	4 (4)	2 (2)	2 (2)
6	0	0	1 (1)
IL28B, n (%)			
CC	20 (22)	22 (25)	20 (22)
Non-CC	70 (78)	65 (75)	68 (76)
Missing	0	0	2 (2)
Baseline CPT Score Category, n (%*)			
CPT A [5-6]	3 (3)	6 (7)	7 (8)
CPT B [7-9]	86 (96)	77 (89)	77 (86)
CPT C [10-12]	1 (1)	4 (5)	6 (7)
Baseline MELD Score Category, n (%*)			
< 10	36 (40)	29 (33)	26 (29)
10-15	50 (56)	54 (62)	59 (66)
16-20	3 (3)	4 (5)	5 (6)
21-25	1 (1)	0	0
Prior HCV Treatment Experience, n (%*)			
Treatment-naïve	32 (36)	40 (46)	48 (53)
Treatment experienced	58 (64)	47 (54)	42 (47)
DAA+Peg-IFN+RBV	9/58 (16)	12/47 (26)	7/42 (17)
Peg-IFN+RBV	30/58 (52)	27/47 (57)	28/42 (67)
Other	18/58 (31)	8/47 (17)	7/42 (17)
Missing	1/58 (2)	0	0

Characteristics	EPCLUSA 12 Weeks N = 90	EPCLUSA + RBV 12 Weeks N = 87	EPCLUSA 24 Weeks N = 90
Prior HCV Response, n (%*)			
Nonresponder	38/58 (66)	33/47 (70)	27/42 (64)
Relapse/Breakthrough	15/58 (26)	10/47 (21)	12/42 (29)
Not Applicable	4/58 (7)	4/47 (9)	3/42 (7)
Missing	1/58 (2)	0	0

CPT = Child-Pugh Turcotte; DAA = direct acting antiviral; MELD = model for end stage liver disease; Peg-IFN = pegylated interferon; RBV = ribavirin; SD = standard deviation
*Total percentage may not add to 100% due to rounding.

Study Results

Table 26 presents the SVR12 for the ASTRAL-4 trial by HCV genotype. All 3 treatment groups met their primary efficacy endpoints with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. The p-value was < 0.001 for the comparison with the SVR12 for each treatment group.

Table 26. SVR12 in Study ASTRAL-4 by HCV Genotype

	EPCLUSA 12 Weeks (N = 90) % (n/N)	EPCLUSA + RBV 12 Weeks (N = 87) % (n/N)	EPCLUSA 24 Weeks (N = 90) % (n/N)
Overall SVR12	83 (75/90)	94 (82/87)	86 (77/90)
Genotype 1	88 (60/68)	96 (65/68)	92 (65/71)
Genotype 1a	88 (44/50)	94 (51/54)	93 (51/55)
Genotype 1b	89 (16/18)	100 (14/14)	88 (14/16)
Genotype 3	50 (7/14)	85 (11/13)	50 (6/12)
Genotype 2, 4 and 6	100 (8/8)[a]	100 (6/6)[b]	86 (6/7)[c]

RBV = ribavirin

a. N=4 for genotype 2 and N=4 for genotype 4

b. N=4 for genotype 2 and N=2 for genotype 4

c. N=4 for genotype 2, N=2 for genotype 4 and N=1 for genotype 6.

Note: There were no patients enrolled with genotype 5 infection.

Table 27 presents the SVR12 for genotype 1 or 3 HCV infected patients in the ASTRAL-4 trial by prior treatment.

Table 27. SVR12 for Genotype 1 or 3 HCV Infected Patients in the ASTRAL-4 Trial by Prior Treatment

	EPCLUSA 12 Weeks		EPCLUSA + RBV 12 Weeks		EPCLUSA 24 Weeks	
	GT1 (N = 68) % (n/N)	GT3 (N = 14) % (n/N)	GT1 (N = 68) % (n/N)	GT3 (N = 13) % (n/N)	GT1 (N = 71) % (n/N)	GT3 (N = 12) % (n/N)
Treatment-naive	92 (22/24)	50 (3/6)	93 (25/27)	80 (8/10)	89 (33/37)	60 (3/5)
Treatment Experienced	86 (38/44)	50 (4/8)	98 (40/41)	100 (3/3)	94 (32/34)	43 (3/7)

Table 28 presents the virologic outcome for patients with genotype 1 or 3 HCV in the ASTRAL-4 trial. No patients with genotype 2, 4 or 6 HCV experienced virologic failure.

Table 28. Virologic Failure for Patients with Genotype 1 and 3 HCV in ASTRAL-4 Trial

	EPCLUSA 12 Weeks (N = 82) % (n/N)	EPCLUSA + RBV 12 Weeks (N = 81) % (n/N)	EPCLUSA 24 Weeks (N = 83) % (n/N)
Virologic Failure (relapse and on-treatment failure)			
Genotype 1[a]	7 (5/68)	1 (1/68)	4 (3/71)
Genotype 1a	6 (3/50)	2 (1/54)	4 (2/55)
Genotype 1b	11 (2/18)	0 (0/14)	6 (1/16)
Genotype 3	43 (6/14)	15 (2[b]/13)	42 (5[c]/12)

RBV = ribavirin

a. No patients with genotype 1 HCV had on- treatment virologic failure.

b. One patient had on-treatment virologic failure; PK data for this patient was consistent with non-adherence.

c. One patient had on-treatment virologic failure.

The overall SVR12 (virologic cure) in ASTRAL-4 for the recommended treatment regimen was 94% (82/87).

Changes in MELD and CPT score from baseline to post-treatment Week 12 (secondary endpoint) were analyzed for patients who achieved SVR12 and for whom data were available (N = 234) to assess the effect of SVR12 on hepatic function post-treatment. Of the 82 subjects treated with EPCLUSA + RBV for 12 weeks who achieved SVR12, 81 had MELD and CPT assessments at baseline and post-treatment week 12.

Change in MELD score: Among those who achieved SVR12 with 12 weeks treatment with EPCLUSA + RBV, 51% (41/81) and 15% (12/81) had an improvement or no change in MELD score from baseline to post-treatment week 12, respectively; of the 10 patients whose MELD score was ≥ 15 at baseline, 40% (4/10) had a MELD score < 15 at post-treatment Week 12. Improvement in MELD score was due to improvement (decreases) in bilirubin.

Change in CPT: Among those who achieved SVR12 with 12 weeks treatment with EPCLUSA + RBV, 41% (33/81) and 49% (40/81) had an improvement or no change of CPT scores from baseline to post-treatment week 12, respectively. Of the 72 patients who had CPT B cirrhosis at baseline, 11% (8/72) had CPT A cirrhosis at post-treatment Week 12. Improvement in CPT score was due to improvements in albumin (increases) and bilirubin (decreases).

Similar proportions of subjects treated with EPCLUSA for 12 or 24 weeks had improvements in MELD and CPT scores compared with subjects treated with EPCLUSA + RBV for 12 weeks.

MICROBIOLOGY

Antiviral Activity in Cell Culture

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 29. The EC_{50} values of sofosbuvir and velpatasvir against clinical isolates are presented in Table 30.

Table 29. 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	NA	0.004
5a	15[b]	0.021-0.054[d]
6a	14[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 replicon or chimeric NS5A replicons carrying full-length NS5A gene that contains L31 or M31 polymorphisms.

d. Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

Table 30. 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	15	29 (14-81)	8	0.011 (0.006-0.364)
2b	NA	NA	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

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 primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a, and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In vitro selection of HCV replicons with reduced susceptibility to velpatasvir was performed in cell culture for multiple genotypes including 1a, 1b, 2a, 3a, 4a, 5a, and 6a. Variants were selected at NS5A resistance associated positions 24, 28, 30, 31, 32, 58, 92, and 93. The resistance associated variants (RAVs) selected in 2 or more genotypes were F28S, L31I/V, and Y93H. From site-directed mutagenesis studies, NS5A RAVs that showed a > 2.5-fold reduction in velpatasvir susceptibility are listed in Table 31 below. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a > 100-fold reduction in velpatasvir susceptibility (see **MICROBIOLOGY**, **Resistance**, **In Clinical Trials**, Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome). Combinations of these variants often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

Table 31. Phenotypic Change of Genotype 1-6 NS5A Substitutions to Velpatasvir

Genotype	> 2.5-100-fold*	> 100-fold*
1a	M28A/T, Q30E/G/K, L31F/I/M/V, P32L, H58D, Y93C/L/S/T	M28G, A92K, Y93H/N/R/W
1b	Q24K, L31F/I, P58T, Y93H/N/T	A92K
2a	F28S, L31V, C92R, Y93H/N	None
2b	L28F, P58A, C92S, Y93F	C92T, Y93H/N
3a	A30H/K, L31F/M, P58G	Y93H
4a	L28T, Y93H/N/S	None
5a	L31I	None
6a	F28M/V, L31I/M, T58G/H, A92T, T93A/H/N/S	L31V, P32A/L/Q/R

*Fold change was calculated as the ratio of mutant EC_{50} to wild-type EC_{50}.

In Clinical Trials

Studies in Patients with Compensated Liver Disease

In a pooled analysis of patients without cirrhosis or with compensated cirrhosis who received EPCLUSA for 12 weeks in Phase 3 trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3), 12 patients (2 with genotype 1 and 10 with genotype 3) qualified for resistance analysis due to virologic failure. One additional virologic failure patient with genotype 3 HCV infection at baseline was reinfected with genotype 1a HCV at virologic failure and was excluded from the virological analysis. No patients with genotype 2, 4, 5, or 6 HCV infection experienced virologic failure.

Of the two genotype 1 virologic failure patients, one patient had virus with emergent NS5A RAV Y93N and the other patient had virus with emergent NSA RAVs L31I/V and Y93H at virologic failure. Both patients had virus at baseline harboring NS5A RAVs. No NS5B nucleoside inhibitor (NI) RAVs were observed at failure in the two patients.

Of the ten genotype 3 virologic failure patients, Y93H was observed in all 10 patients at failure (6 had Y93H emerge post-treatment and 4 patients had Y93H at baseline and post-treatment). No NS5B NI RAVs were observed at failure in the ten patients.

Studies in Patients with Decompensated Cirrhosis

In the ASTRAL-4 trial in patients with decompensated cirrhosis who received EPCLUSA + RBV for 12 weeks, 3 patients (one with genotype 1 and two with genotype 3) qualified for resistance analysis due to virologic failure. No patients with genotype 2 or 4 HCV infection in the EPCLUSA + RBV 12 Weeks group experienced virologic failure.

The one virologic failure patient with genotype 1 HCV had no NS5A or NS5B RAVs at failure.

Of the two genotype 3 virologic failure patients, one had NS5A RAV Y93H emerge at failure. Another patient had virus with Y93H at baseline and virologic failure and also developed low levels (< 5%) of NS5B NI RAVs N142T and E237G at failure. Pharmacokinetic data of this patient was consistent with non-adherence.

In the ASTRAL-4 trial, two patients treated with EPCLUSA for 12 or 24 weeks without ribavirin had emergent NS5B S282T at low levels (< 5%) along with L159F.

Effect of Baseline HCV Resistance Associated Variants on Treatment Outcome

Studies in Patients with Compensated Liver Disease

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients without cirrhosis or with compensated cirrhosis (ASTRAL-1, ASTRAL-2, and ASTRAL-3). Of the 1035 patients treated with EPCLUSA in the ASTRAL-1, ASTRAL-2, and ASTRAL-3 studies, 1023 patients were included in the analysis of NS5A RAVs; 7 subjects were excluded as they neither achieved SVR12 nor had virologic failure and 5 additional patients were excluded as NS5A gene sequencing failed. In the pooled analysis of the Phase 3 trials, 380/1023 (37%) patients' virus had baseline NS5A RAVs. Genotype 2, 4, and 6 HCV infected patients had a higher prevalence of NS5A RAVs (70%, 63% and 52%, respectively) compared to genotype 1 (23%), genotype 3 (16%), and genotype 5 (18%) HCV infected patients.

SVR12 in patients with or without baseline NS5A RVAs in ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials is shown in Table 32.

Table 32. SVR12 in Patients with or without Baseline NS5A RAVs by HCV Genotype (ASTRAL-1, ASTRAL-2, ASTRAL-3)

	EPCLUSA 12 Weeks			
SVR12	Genotype 1	Genotype 3	Genotype 2, 4, 5 or 6	Total
With any baseline NS5A RAVs	97% (73/75)	88% (38/43)	100% (262/262)	98% (373/380)
Without baseline NS5A RAVs	100% (251/251)	97% (225/231)	100% (161/161)	99% (637/643)

RAVs = resistance associated variants; RBV = ribavirin; SVR = sustained virologic response

Among the 75 genotype 1 patients who had baseline NS5A RAVs, SVR12 was 97% (67/69) and 100% (6/6) in patients with baseline NS5A RAVS that confer ≤ 100-fold and > 100-fold reduced susceptibility to velpatasvir, respectively. Among the 43 genotype 3 patients who had baseline

NS5A RAVs, SVR12 was 94% (15/16) and 85% (23/27) in patients with NS5A RAVS that confer ≤ 100-fold and > 100-fold reduced susceptibility to velpatasvir, respectively. The four genotype 3 patients who had baseline NS5A RAVs conferring >100-fold reduced susceptibility to velpatasvir and failed to achieve SVR12 all had NS5A substitution Y93H at baseline. Twenty-one of 25 genotype 3 patients with baseline NS5A substitution Y93H achieved SVR12.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 trials. SVR12 was achieved in all 77 patients who had baseline NS5B NI RAVs including N142T, L159F, E/N237G, C/M289L/I, L320F/I/V, V321A/I, and S282G+V321I.

Studies in Patients with Decompensated Cirrhosis

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients with decompensated cirrhosis (ASTRAL-4). Of the 87 patients treated with EPCLUSA + RBV in the ASTRAL-4 study, 85 patients were included in the analysis of NS5A RAVs; 2 patients were excluded as they neither achieved SVR12 nor had virologic failure. Among the patients who received treatment with EPCLUSA + RBV for 12 weeks, 29% (25/85) of patients had baseline virus with NS5A RAVs [29% (19/66), 75% (3/4), 15% (2/13), and 50% (1/2) for patients with genotype 1, 2, 3 and 4 HCV, respectively].

SVR12 in patients with or without baseline NS5A RAVs in the EPCLUSA + RBV 12 week group of ASTRAL-4 trial is shown in Table 33.

Table 33. SVR12 in Patients with or without Baseline NS5A RAVs by HCV Genotype (ASTRAL-4)

	EPCLUSA + RBV 12 Weeks			
	Genotype 1	Genotype 3	Genotype 2 or 4	Total
With any baseline NS5A RAVs	100% (19/19)	50% (1/2)	100% (4/4)	96% (24/25)
Without baseline NS5A RAVs	98% (46/47)	91% (10/11)	100% (2/2)	98% (58/60)

RAVs = resistance associated variants; RBV = ribavirin

The single genotype 3 patient who had baseline NS5A RAVs and failed to achieve SVR12 had NS5A substitution Y93H at baseline and the pharmacokinetic data of this patient was consistent with non-adherence.

Three patients in the EPCLUSA + RBV 12 week group had baseline NS5B NI RAVs (N142T and L159F) and all three patients achieved SVR12.

Cross Resistance

Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. *In vitro* data suggests that the majority of NS5A RAVs that confer resistance to ledipasvir and daclatasvir remained susceptible to velpatasvir. Velpatasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all velpatasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and velpatasvir were fully active against substitutions associated with resistance to other classes of direct acting antivirals with different mechanisms of actions, 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.

TOXICOLOGY

Repeat-Dose Toxicity

Sofosbuvir

Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, was evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary sofosbuvir target organs identified were the gastrointestinal (GI) and hematopoietic (erythroid) systems. In a 7-day toxicity dog study with GS-9851, a dose of 1500 mg/kg/day resulted in (but were not limited to) increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings and increased QT/QTc intervals in dogs. At the adverse dose, GS-331007 exposure levels in the dog study were at least 63-fold higher than HCV-infected subjects treated once daily with EPCLUSA. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), sofosbuvir effects included (but were not limited to) GI-related clinical signs (e.g., soft feces and emesis) and a decrease (e.g., approximately 10%) in mean red cell indices that were observed mainly in the high-dose group of dogs. One male dog was euthanized moribund with intestinal hemorrhage. The relationship to sofosbuvir was undetermined. In general, exposure levels in the chronic toxicity studies at the no observed adverse effect level were at least 5-fold (based on AUC of GS-331007) higher than HCV-infected subjects treated once daily with EPCLUSA.

Velpatasvir

Velpatasvir was well tolerated in studies for up to 4 weeks in the mouse, 26 weeks in the rat, and 39 weeks in the dog. No target organs were identified at the highest dose evaluated in each respective repeat dose toxicity study, corresponding to exposure margins of 74-, 5-, and 10-fold greater in mice, rats, and dogs, respectively, than those in HCV-infected subjects treated once daily with EPCLUSA.

Genotoxicity and Carcinogenicity

Sofosbuvir

Sofosbuvir, when administered as the diastereomeric mixture GS-9851, was not genotoxic in a bacterial mutagenicity assay, in an *in vitro* chromosome aberration test using human peripheral blood lymphocytes and in an *in vivo* mouse micronucleus assay.

Sofosbuvir was not carcinogenic in the 2-year mouse and rat carcinogenicity studies at doses resulting in GS-331007 exposures up to 15-times in mice and 9-times in rats, higher than human exposure at 400 mg dose.

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 with velpatasvir are ongoing.

Fertility

Sofosbuvir

Sofosbuvir had no effects on fertility when evaluated in rats at exposures (AUC) to the predominant circulating metabolite GS-331007 of at least 4-fold the exposure in humans at the recommended clinical dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through lactation day 20 at daily GS-331007 exposures of approximately 6-fold higher than human exposures at the recommended clinical dose.

Velpatasvir

Velpatasvir had no adverse effects on fertility in rats at AUC exposure 6-fold higher than the human exposure at the recommended clinical dose.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrEPCLUSA™
sofosbuvir and velpatasvir tablets

Read this carefully before you start taking **Epclusa**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment. Ask whether there is any new information about **Epclusa**.

What is Epclusa used for?
- **Epclusa** treats chronic (lasting longer than 6 months) hepatitis C infection in adults.
- Your doctor may decide to prescribe **Epclusa** in combination with ribavirin.
- **Epclusa** cures chronic hepatitis C in most patients. Cure means that there is no virus left in the body. This is confirmed with a blood test 3 months after the end of treatment.
- Do NOT give to children under 18 years of age. It is not known if **Epclusa** is safe or works in children.

How does Epclusa work?
Epclusa contains two medicines, sofosbuvir and velpatasvir, that have been combined together into one tablet (pill). This type of treatment course (regimen) is also known as a single tablet regimen. It provides a complete treatment for hepatitis C. For most patients, **Epclusa** does not need to be taken with ribavirin.

- Sofosbuvir and velpatasvir block the virus from making additional copies of itself. They work together to help prevent viral growth, thereby reducing the infection and allowing the body to clear (remove) the virus from the blood and liver.
- Curing chronic hepatitis C virus can help reduce the risk of illness and death caused by liver disease.

What are the ingredients in Epclusa?
Medicinal ingredients: Sofosbuvir, Velpatasvir
Non-medicinal ingredients: Copovidone, croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The coating of the tablets contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

Epclusa comes in the following dosage forms:
Epclusa comes in tablets. Each tablet contains sofosbuvir (400 milligrams) and velpatasvir (100 milligrams). **Epclusa** tablets are pink. They have a diamond shape. The tablets say “GSI” on one side and “7916” on the other side. Each bottle contains 28 tablets. The bottle has a cap that children cannot open. The bottle also contains some polyester coil (which looks white and fluffy). Do NOT eat the coil. It is meant to keep your medicine fresh.

Do not use Epclusa if:

- You are allergic to velpatasvir, sofosbuvir (also called **Sovaldi**® when it is used with other medicines without velpatasvir or ledipasvir), or any of the other ingredients in this product. (Read also "**What are the ingredients in Epclusa?**" above.)
- You are taking **Epclusa** in combination with ribavirin and you are pregnant or may become pregnant or if you are a man whose female partner(s) is (are) pregnant or may become pregnant.

To help avoid side effects and ensure you take your medicine properly, talk to your doctor before you take Epclusa. Talk about any health conditions or problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- have had a recent liver transplant.
- have hepatitis B.
- have HIV.
- have severe kidney disease or you are on dialysis.
- are breastfeeding or plan to breastfeed. Do NOT breastfeed while taking **Epclusa**.
- are taking anything listed in the section "**The following may interact with Epclusa**".

- Your doctor may monitor your liver function during **Epclusa** treatment, under some conditions.

Pregnancy:

- If you are pregnant or plan to become pregnant, ask your doctor for advice before taking this medicine. It is NOT known if **Epclusa** can harm your unborn child.
- You or your partner must not become pregnant while taking **Epclusa** in combination with ribavirin or become pregnant within 6 months after you have stopped taking ribavirin. Ribavirin may cause birth defects and death of the fetus. Extreme care must be taken to avoid becoming pregnant.
- Your doctor will order monthly pregnancy test during treatment with **Epclusa** in combination with ribavirin and for 6 months after treatment has stopped.
- If you or your partner become pregnant while taking **Epclusa** in combination with ribavirin, contact your doctor. Read the package insert for ribavirin for information regarding pregnancy.

Contraception:

- If you are taking **Epclusa** in combination with ribavirin, then you and your partner must use 2 effective methods of birth control during the entire treatment and for 6 months after you stop taking this combination.

Another warning you should know about:
Because **Epclusa** already contains sofosbuvir, do not take **Epclusa** with any other medicines containing sofosbuvir (e.g. **Sovaldi**, **Harvoni**®).

Tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Epclusa:

- amiodarone (Cordarone®), a drug used to treat certain abnormal heart rhythms. Amiodarone may slow your heartbeat. Get medical help right away if you get symptoms such as fainting, dizziness, lightheadedness, weakness, shortness of breath.
- carbamazepine (Tegretol®), a drug used to treat seizures, nerve pain, and bipolar disorder.
- digoxin (Lanoxin®, Toloxin®), a drug used to treat congestive heart failure and a certain abnormal heart rhythm (atrial fibrillation).
- efavirenz (Sustiva®, **Atripla**®), a drug used to treat HIV.
- medicines for indigestion, heartburn, or ulcers. Examples are nizatidine (Axid®), famotidine (Pepcid AC®, Peptic Guard®, Ulcidine®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec®), rabeprazole (Aciphex®) and pantoprazole (Pantoloc®) or antacids (like Tums®, Rolaids® or Alka-Seltzer®) that have an ingredient to protect the stomach.
- oxcarbazepine (Trileptal®), a drug used to control seizures.
- phenobarbital, a drug used to treat anxiety and to control seizures.
- phenytoin (Dilantin®), a drug used to control seizures.
- rifabutin (Mycobutin®), a drug used to treat tuberculosis.
- rifampin (Rifadin®, Rifater®, Rofact®), a drug used to treat tuberculosis.
- rosuvastatin (Crestor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety or depression.
- tipranavir (Aptivus®) or tipranavir/ritonavir (Aptivus® and Norvir®), drugs used to treat HIV.
- tenofovir disoproxil fumarate (**Atripla**, **Complera**®, **Stribild**®, **Truvada**®, **Viread**®), to treat HIV.

How to take Epclusa:

- Take this medicine with or without food.
- This medicine is taken for 12 weeks.
- If you are taking an antacid, you may need to take **Epclusa** at a different time than the antacid. Talk to your doctor or pharmacist.
- Do NOT stop taking **Epclusa** without first talking with your doctor.

Usual adult dose:

- Take one tablet once each day.

Overdose:

If you think you have taken too much **Epclusa**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

It is important to take **Epclusa** each day.

- **If you miss a dose** of **Epclusa** and you notice within 18 hours, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Epclusa** and you notice after 18 hours, wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What to do if you vomit (throw up):

- If you vomit **less than 3 hours** after taking **Epclusa**, take another tablet.
- If you vomit **more than 3 hours** after taking **Epclusa**, wait. Do NOT take another tablet until you are scheduled to take the next tablet.

What are possible side effects from using Epclusa?
The most common side effects of **Epclusa** are tiredness and headache.

These are not all the possible side effects you may feel when taking **Epclusa**. If you experience any side effects not listed here, contact your doctor.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your doctor.

Reporting side effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store **Epclusa** below 30 ^{o}C (86 ^{o}F).
- Keep **Epclusa** in its original container.
- Do NOT use **Epclusa** if the seal over the bottle opening is broken or missing.
- Keep this medication where children cannot reach it or see it.

If you want more information about Epclusa:

- Talk to your doctor or pharmacist.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.gilead.ca), or by calling 1-800-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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Gilead Sciences, Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 2W3

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