Product Information
EPCLUSA® (sofosbuvir/velpatasvir) tablets

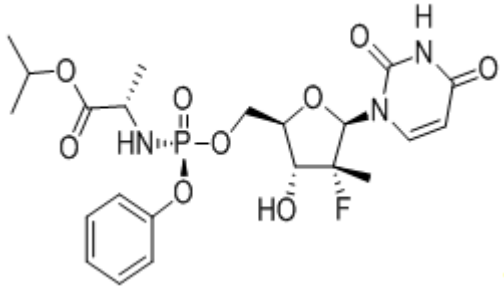
NAME OF THE MEDICINE

EPCLUSA (sofosbuvir/velpatasvir 400 mg/100 mg) tablets.

The active substances in EPCLUSA tablets are sofosbuvir and velpatasvir.

Sofosbuvir is a nucleotide inhibitor of HCV NS5B RNA-dependent RNA polymerase and velpatasvir is an HCV NS5A inhibitor.

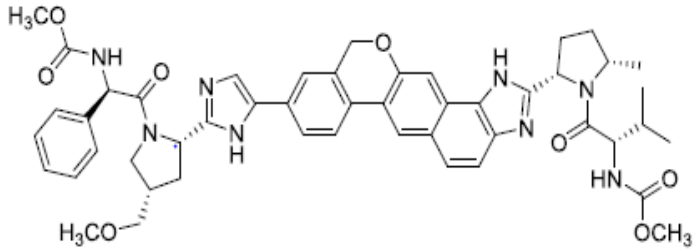
The chemical name of sofosbuvir is (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of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



CAS registry number: 1190307-88-0

Sofosbuvir is a white to off-white powder with a solubility of ≥ 2 mg/mL across the pH range of 2-7.7 at 37 °C. The partition coefficient (log P) for sofosbuvir is 1.62 and the pKa is 9.3.

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



CAS registry number: 1377049-84-7

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

DESCRIPTION

EPCLUSA tablets contain the following ingredients as <u>excipients:</u>

Tablet core: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

Film-coating: polyvinyl alcohol, macrogol 3350, titanium dioxide, talc-purified, and iron oxide red.

Each EPCLUSA tablet is film-coated and pink in colour. The tablets are diamond shaped debossed with "GSI" on one side and the number "7916" on the other side. The tablets are supplied in bottles with child-resistant closures.

PHARMACOLOGY

Pharmacotherapeutic group: Antivirals for systemic use; direct acting antivirals, other antivirals, ATC code: not yet assigned.

Mechanism of action

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

Velpatasvir is a 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.

Antiviral activity *in vitro*

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 1. The EC_{50} values of sofosbuvir and velpatasvir against chimeric replicons representing clinical isolates are presented in Table 2.

Table 1. 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

Replicon Genotype	Sofosbuvir EC_{50}, nM[a]	Velpatasvir EC_{50}, nM[a]
6e	NA	0.130[d]

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

Table 2. 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

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir, but reduced the anti-HCV activity of velpatasvir by 13-fold against genotype 1a HCV replicons.

Evaluation of sofosbuvir in combination with velpatasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Drug 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 genotype 1 to 6 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, the ability of the active triphosphate of sofosbuvir (GS-461203) to inhibit recombinant NS5B polymerase from genotypes 1b, 2a, 3a, and 4a expressing the S282T

substitution was reduced compared to its ability to inhibit wild-type recombinant NS5B polymerase, as indicated by a 8.5- to 24-fold increase in IC_{50}.

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. Site-directed mutagenesis of known NS5A RAVs showed that substitutions conferring a >100-fold reduction in velpatasvir susceptibility are M28G, A92K, and Y93H/N/R/W in genotype 1a, A92K in genotype 1b, C92T and Y93H/N in genotype 2b, Y93H in genotype 3, and L31V and P32A/L/Q/R in genotype 6. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a >100 fold reduction in velpatasvir susceptibility. Combinations of these variants often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

In Clinical Trials:

Studies in Patients without Cirrhosis and Patients with Compensated Cirrhosis

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 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 2 genotype 1 virologic failure patients, 1 patient had virus with emergent NS5A RAV Y93N and the other patient had virus with emergent NS5A 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 10 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 10 patients.

Studies in Patients with Decompensated Cirrhosis

In the ASTRAL-4 trial, in patients with decompensated cirrhosis who received EPCLUSA + ribavirin (RBV) for 12 weeks, 3 patients (1 with genotype 1 and 2 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 1 virologic failure patient with genotype 1 HCV had no NS5A or NS5B RAVs at failure.

Of the 2 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 from this patient was consistent with non-adherence.

In the ASTRAL-4 trial, 2 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 without Cirrhosis and Patients with Compensated Cirrhosis

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 trials, 1023 patients were included in the analysis of NS5A RAVs; 7 patients were excluded as they neither achieved sustained virologic response (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 RAVs in ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials is shown in Table 3.

Table 3. Studies ASTRAL-1, ASTRAL-2, and ASTRAL-3: SVR12 in Patients With or Without Baseline NS5A RAVs by HCV Genotype

	EPCLUSA 12 Weeks			
	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)

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 4 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 (84%) 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 trial, 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 4.

Table 4. Study ASTRAL-4: SVR12 in Patients With or Without Baseline NS5A RAVs by HCV Genotype

	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)

The single genotype 3 patient who had baseline NS5A RAVs and failed to achieve SVR12 had NS5A substitution Y93H at baseline; pharmacokinetic data from 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

In vitro data suggest 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.

Pharmacokinetics

Absorption

The pharmacokinetic properties of sofosbuvir, GS-331007 (the predominant circulating metabolite of sofosbuvir), and velpatasvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration of EPCLUSA, sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 0.5-1.0 hour post-dose. Median peak plasma concentration of GS-331007 was observed 3.0 hours post-dose. Velpatasvir median peak concentrations were observed 3.0 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected patients, mean steady-state AUC_{0-24} for sofosbuvir (N=982), GS-331007 (N=1428), and velpatasvir (N=1425) were 1260, 13970, and 2970 ng•hr/mL, respectively. Steady-state C_{max} for sofosbuvir, GS-331007, and velpatasvir were 566, 868, and 259 ng/mL, respectively. 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.

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. Sofosbuvir and velpatasvir are substrates for both P-gp and breast cancer resistance protein (BCRP)-mediated transport.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 mg/mL to 20 mg/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 mg/mL to 1.8 mg/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 metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. 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 approximately > 90% of total systemic exposure.

Velpatasvir is a substrate of CYP2B6, CYP2C8, and CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-velpatasvir, the majority (> 98%) of radioactivity in plasma was parent drug. Monohydroxylated and desmethylated velpatasvir were the metabolites identified in human plasma. Unchanged velpatasvir is the major species present in faeces.

Excretion

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the [^{14}C]-radioactivity was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of EPCLUSA were 0.5 and 25 hours, respectively.

Following a single 100 mg oral dose of [^{14}C]-velpatasvir, mean total recovery of the [^{14}C]-radioactivity was 95%, consisting of approximately 94% and 0.4% recovered from the faeces and urine, respectively. Unchanged velpatasvir was the major species in faeces accounting for a mean of 77% of the administered dose, followed by monohydroxylated velpatasvir (5.9%) and desmethylated velpatasvir (3.0%). These data indicate that 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.

Effect of Food

Relative to fasting conditions, the administration of a single dose of EPCLUSA with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal increased sofosbuvir $AUC_{0\text{-}inf}$ by 60% and 78%, respectively, but did not substantially affect the sofosbuvir C_{max}. The moderate- or high-fat meal did not alter GS-331007 $AUC_{0\text{-}inf}$, but resulted in a 25% and 37% decrease in C_{max}, respectively. The moderate or high fat meal resulted in a 34% and 21% increase in velpatasvir $AUC_{0\text{-}inf}$, respectively, and a 31% and 5% increase in velpatasvir C_{max}, respectively. 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.

Special Populations

Race and Gender

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

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

Elderly Patients

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 82 years) analysed, 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 (12% of total number of patients in the Phase 3 clinical trials). The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

Paediatric Patients

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

Patients with Impaired Renal Function

The pharmacokinetics of sofosbuvir were studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73m^2), moderate (eGFR ≥ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and patients with end stage renal disease (ESRD) requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88%, and 451% higher, respectively. In patients with ESRD, sofosbuvir $AUC_{0\text{-}inf}$ was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when dosed 1 hour after haemodialysis, respectively. The $AUC_{0\text{-}inf}$ of GS-331007 in patients with ESRD administered with sofosbuvir 1 hour before or 1 hour after haemodialysis was at least 10-fold and 20-fold higher, respectively. GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400 mg dose of sofosbuvir, a 4 hour haemodialysis removed 18% of administered dose. No dose adjustment is required for patients with mild or moderate renal impairment. The

safety and efficacy of sofosbuvir have not been established in patients with severe renal impairment or ESRD.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). No clinically relevant differences in velpatasvir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment. No dose adjustment of velpatasvir is required for patients with mild, moderate, or severe renal impairment.

Patients with Hepatic Impairment

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 patients 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. 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. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate, and severe hepatic impairment.

The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative patients with moderate and severe hepatic impairment (Child Pugh Class B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in patients with moderate hepatic impairment, severe hepatic impairment, and control patients 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. No dose adjustment of velpatasvir is required for patients with mild, moderate, or severe hepatic impairment.

Assessment of Drug Interactions

After oral administration of EPCLUSA, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. Hydrolytic prodrug cleavage and sequential phosphorylation steps results in formation of the pharmacologically active uridine nucleoside analog triphosphate. Dephosphorylation of nucleotide metabolites results in conversion to the predominant circulating metabolite GS-331007 that accounts for approximately 85% of total systemic exposure. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP, while GS-331007 is not. Velpatasvir is poorly transported by OATP1B1 and OATP1B3. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OCT1, and GS-331007 is not an inhibitor of OAT1, OAT3, OCT2, and MATE1. Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Velpatasvir is an inhibitor of drug transporter P-gp, BCRP, OATP1B1, and OATP1B3, and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant concentration, velpatasvir is not an inhibitor of hepatic

transporters OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

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

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

Co-administered Drug	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir, GS-331007 and Velpatasvir PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF	300/100 + 200/300 once daily	100 once daily	400 once daily	24	sofosbuvir	1.12 (0.97, 1.29)	1.22 (1.12, 1.33)	NA
					GS-331007	1.21 (1.12, 1.29)	1.32 (1.27, 1.36)	1.42 (1.37, 1.49)
					velpatasvir	1.55 (1.41, 1.71)	2.42 (2.23, 2.64)	4.01 (3.57, 4.50)
Cyclosporine	600 single dose	ND	400 single dose	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
		100 single dose	ND	12	velpatasvir	1.56 (1.22, 2.01)	2.03 (1.51, 2.71)	NA
Darunavir/ ritonavir + emtricitabine/ tenofovir DF	800/100 + 200/300 once daily	100 once daily	400 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	100 once daily	400 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	100 once daily	400 once daily	14	sofosbuvir	1.38 (1.14, 1.67)	0.97 (0.83, 1.14)	NA
					GS-331007	0.86 (0.80, 0.93)	0.90 (0.85, 0.96)	1.01 (0.95, 1.07)
					velpatasvir	0.53 (0.43, 0.64)	0.47 (0.39, 0.57)	0.43 (0.36, 0.52)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide[c]	150/150/200/ 10 once daily	100 once daily	400 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/	150/150/200/ 300 once	100 once daily	400 once daily	24	sofosbuvir	1.01 (0.85, 1.19)	1.24 (1.13, 1.37)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir 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}
emtricitabine/ tenofovir DF[d]	daily				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	100 once daily	400 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)
Famotidine	40 single dose simultaneously with EPCLUSA	100 single dose	400 single dose	60	sofosbuvir	0.92 (0.82, 1.05)	0.82 (0.74, 0.91)	NA
					GS-331007	0.84 (0.78, 0.89)	0.94 (0.91, 0.98)	NA
					velpatasvir	0.80 (0.70, 0.91)	0.81 (0.71, 0.91)	NA
	40 single dose 12 hours prior to EPCLUSA			60	sofosbuvir	0.77 (0.68, 0.87)	0.80 (0.73, 0.88)	NA
					GS-331007	1.20 (1.13, 1.28)	1.04 (1.01, 1.08)	NA
					velpatasvir	0.87 (0.76, 1.00)	0.85 (0.74, 0.97)	NA
Ketoconazole	200 twice daily	100 single dose	ND	12	velpatasvir	1.29 (1.02, 1.64)	1.71 (1.35, 2.18)	NA
Lopinavir/ ritonavir + emtricitabine/ tenofovir DF	4 x 200/50 + 200/300 once daily	100 once daily	400 once daily	24	sofosbuvir	0.59 (0.49, 0.71)	0.71 (0.64, 0.78)	NA
					GS-331007	1.01 (0.98, 1.05)	1.15 (1.09, 1.21)	1.15 (1.07, 1.25)
					velpatasvir	0.70 (0.59, 0.83)	1.02 (0.89, 1.17)	1.63 (1.43, 1.85)
Methadone	30 to 130 daily	ND	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA
Omeprazole	20 once daily simultaneously with EPCLUSA	100 single dose fasted	400 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	100 single dose fasted	400 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	100 single dose fed	400 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

Co-administered Drug	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir 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}
	EPCLUSA				velpatasvir	0.52 (0.43, 0.64)	0.62 (0.51, 0.75)	NA
	20 once daily 4 hours after EPCLUSA	100 single dose fed	400 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	100 single dose fed	400 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
Raltegravir + emtricitabine/ tenofovir DF	400 twice daily + 200/300 once daily	100 once daily	400 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)
Rifampin	600 once daily	ND	400 single dose	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
		100 single dose	ND	12	velpatasvir	0.29 (0.23, 0.37)	0.18 (0.15, 0.22)	NA
	600 single dose	100 single dose	ND	12	velpatasvir	1.28 (1.05, 1.56)	1.46 (1.17, 1.83)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available/not applicable, ND = not dosed.
a. All interaction studies conducted in healthy volunteers.
b. Administered as Atripla (efavirenz, emtricitabine and tenofovir DF fixed-dose combination).
c. Administered as Genvoya (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fixed-dose combination).
d. Administered as Stribild (elvitegravir, cobicistat, emtricitabine and tenofovir DF fixed-dose combination).
e. Administered as Complera (emtricitabine, rilpivirine and tenofovir DF fixed-dose combination).

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

Co-administered Drug	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered Drug PK With/Without Sofosbuvir, Velpatasvir or EPCLUSA No Effect=1.00		
					C_{max}	AUC	C_{min}
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF[b]	atazanavir 300 once daily	100 once daily	400 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)

Co-administered Drug	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir 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}
	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)
Cyclosporine	600 single dose	100 single dose	ND	12	0.92 (0.82, 1.02)	0.88 (0.78, 1.00)	NA
		ND	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
Darunavir/ritonavir + emtricitabine/ tenofovir DF[c]	darunavir 800 once daily	100 once daily	400 once daily	29	0.90 (0.86, 0.95)	0.92 (0.87, 0.98)	0.87 (0.79, 0.95)
	ritonavir 100 once daily				1.07 (0.97, 1.17)	1.12 (1.05, 1.19)	1.09 (1.02, 1.15)
	emtricitabine 200 once daily				1.05 (1.01, 1.08)	1.05 (1.02, 1.08)	1.04 (0.98, 1.09)
	tenofovir DF 300 once daily				1.55 (1.45, 1.66)	1.39 (1.33, 1.44)	1.52 (1.45, 1.59)
Digoxin	0.25 single dose	100	ND	21	1.88 (1.71, 2.08)	1.34 (1.13, 1.60)	NA
Dolutegravir	50 mg once daily	100 once daily	400 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	100 once daily	400 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/ cobicisat/ emtricitabine/ tenofovir alafenamide[e]	elvitegravir 150 once daily	100 once daily	400 once daily	24	0.87 (0.80, 0.94)	0.94 (0.88, 1.00)	1.08 (0.97, 1.20)
	cobicistat 150 once daily				1.16 (1.09, 1.23)	1.30 (1.23, 1.38)	2.03 (1.67, 2.48)
	emtricitabine 200 once daily				1.02 (0.97, 1.06)	1.01 (0.98, 1.04)	1.02 (0.97, 1.07)
	tenofovir alafenamide 10 once daily				0.80 (0.68, 0.94)	0.87 (0.81, 0.94)	NA
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir DF[f]	elvitegravir 150 once daily	100 once daily	400 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 once 200 daily	100 once daily	400 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)

Co-administered Drug	Dose of Co-administered Drug (mg)	Velpatasvir Dose (mg)	Sofosbuvir 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}
	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	100 once daily	400 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)
R-Methadone	30 to 130 daily	ND	400 once daily	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone					0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)
Norelgestromin	norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily	100 once daily	ND	13	0.97 (0.88, 1.07)	0.90 (0.82, 0.98)	0.92 (0.83, 1.03)
		ND	400 once daily	15	1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel		100 once daily	ND	13	0.96 (0.78, 1.19)	0.91 (0.73, 1.15)	0.92 (0.73, 1.18)
		ND	400 once daily	15	1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol		100 once daily	ND	12	1.39 (1.17, 1.66)	1.04 (0.87, 1.24)	0.83 (0.65, 1.06)
		ND	400 once daily	15	1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Pravastatin	pravastatin 40 single dose	100 once daily	ND	18	1.28 (1.08, 1.52)	1.35 (1.18, 1.54)	NA
Rosuvastatin	rosuvastatin 10 single dose	100 once daily	ND	18	2.61 (2.32, 2.92)	2.69 (2.46, 2.94)	NA
Raltegravir + emtricitabine/ tenofovir DF	emtricitabine 200 once daily	100 once daily	400 once daily	30	1.08 (1.04, 1.12)	1.05 (1.03, 1.07)	1.02 (0.97, 1.08)
	tenofovir DF 300 once daily				1.46 (1.39, 1.54)	1.40 (1.34, 1.45)	1.70 (1.61, 1.79)
	raltegravir 400 twice daily				1.03 (0.74, 1.43)	0.97 (0.73, 1.28)	0.79 (0.42, 1.48)
Tacrolimus	5 single dose	ND	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	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 combination).
f. Administered as Stribild (elvitegravir, cobicistat, emtricitabine and tenofovir DF fixed-dose combination).
g. Administered as Eviplera (emtricitabine, rilpivirine and tenofovir DF fixed-dose combination).

CLINICAL TRIALS

Description of Clinical Studies

The efficacy of EPCLUSA was evaluated in three Phase 3 trials in patients with genotype 1 to 6 HCV infection with or without compensated cirrhosis and one Phase 3 trial in patients with genotype 1 to 6 HCV infection with decompensated cirrhosis, as summarised in Table 7.

Table 7. Trials Conducted with EPCLUSA in Patients with Genotype 1, 2, 3, 4, 5 or 6 HCV Infection

Trial	Population	Study Arms (Number of Patients Treated)
ASTRAL-1	Genotype 1, 2, 4, 5, and 6 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (134) SOF+RBV 12 weeks (132)
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	EPCLUSA 12 weeks (277) SOF+RBV 24 weeks (275)
ASTRAL-4	Genotype 1, 2, 3,4, 5, and 6 TN and TE, with CPT class B decompensated cirrhosis	EPCLUSA 12 weeks (90) EPCLUSA+RBV 12 weeks (87) EPCLUSA 24 weeks (90)

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

The ribavirin dose was weight-based (1000 mg daily administered in two divided doses for patients < 75 kg and 1200 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 RBV product information. Serum HCV RNA values were measured during the clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU per mL. Sustained virologic response (SVR12), 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.

Clinical Studies in Patients without Cirrhosis and Patients with Compensated Cirrhosis

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

ASTRAL-1 was a randomised, double-blind, placebo-controlled trial that evaluated 12 weeks of treatment with EPCLUSA compared with 12 weeks of placebo in patients with genotype 1, 2, 4, 5, or 6 HCV infection. Patients with genotype 1, 2, 4, or 6 HCV infection were randomised in a 5:1 ratio to treatment with EPCLUSA for 12 weeks or placebo for 12 weeks. Patients with genotype 5 HCV infection were enrolled to the EPCLUSA group. Randomisation was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of cirrhosis.

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

Table 8 presents the SVR12 and other virologic outcomes in EPCLUSA treated patients in the ASTRAL-1 trial by HCV genotype. No patients in the placebo group achieved SVR12.

Table 8. Study ASTRAL-1: SVR12 and Virologic Outcomes by HCV Genotype

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

a The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Genotype 2 HCV Infected Adults (ASTRAL-2)

ASTRAL-2 was a randomised, open-label trial that evaluated 12 weeks of treatment with EPCLUSA compared with 12 weeks of treatment with SOF+RBV in patients with genotype 2 HCV infection. Patients were randomised in a 1:1 ratio to treatment with EPCLUSA for 12 weeks or SOF+RBV for 12 weeks. Randomisation was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment naïve vs treatment experienced).

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

Table 9 presents the SVR12 and other virologic outcomes from the ASTRAL-2 trial.

Table 9. Study ASTRAL-2: SVR12 and Virologic Outcomes (HCV Genotype 2)

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

a The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

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%).

Genotype 3 HCV Infected Adults (ASTRAL-3)

ASTRAL-3 was a randomised, open-label trial that evaluated 12 weeks of treatment with EPCLUSA compared with 24 weeks of treatment with SOF+RBV in patients with genotype 3 HCV infection. Patients were randomised in a 1:1 ratio to treatment with EPCLUSA for 12 weeks or SOF+RBV for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment naïve vs treatment experienced).

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

Table 10 presents the SVR12 and other virologic outcomes for the ASTRAL-3 trial.

Table 10.Study ASTRAL-3: SVR12 and Virologic Outcomes (HCV Genotype 3)

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

a The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

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%).

SVR12 for selected subgroups are presented in Table 11.

Table 11. Study ASTRAL-3: SVR12 for Selected Subgroups (HCV Genotype 3)

	EPCLUSA 12 Weeks		SOF+RBV 24 Weeks[a]	
	Treatment-Naïve (N=206)	Treatment-Experienced (N=71)	Treatment-Naïve (N=201)	Treatment-Experienced (N=69)
Without cirrhosis	98% (160/163)	91% (31/34)	90% (141/156)	71% (22/31)
With cirrhosis	93% (40/43)	89% (33/37)	73% (33/45)	58% (22/38)

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

Clinical Studies in Patients with Decompensated Cirrhosis

ASTRAL-4

ASTRAL-4 was a randomised, open-label trial in patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection and Child-Pugh B cirrhosis. Patients were randomised in a 1:1:1 ratio to treatment with EPCLUSA for 12 weeks, EPCLUSA+RBV for 12 weeks, or EPCLUSA for 24 weeks. Randomisation was stratified by HCV genotype (1, 2, 3, 4, 5, 6 and indeterminate).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated patients, the median age was 59 years (range: 40 to 73); 70% of the patients were male; 90% were White, 6% were Black; 42% had a baseline body mass index at least 30 kg/m^2; The proportions of patients with genotype 1, 2, 3, 4, or 6 HCV were 78%, 4%, 15%, 3%, and <1% (1 patient), respectively. No patients with genotype 5 HCV infection were enrolled. 76% had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels at least 800,000 IU/mL; 55% were treatment-experienced; 90% and 95% of patients had CPT B cirrhosis and Model for End Stage Liver Disease (MELD) score ≤15 at baseline, respectively.

Table 12 presents the SVR12 for the ASTRAL-4 trial by HCV genotype.

Table 12. Study ASTRAL-4: SVR12 by HCV Genotype

	EPCLUSA 12 Weeks (N=90)	EPCLUSA+RBV 12 Weeks (N=87)	EPCLUSA 24 Weeks (N=90)
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]

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.

Table 13 presents the virologic outcome for patients with genotype 1 or 3 HCV infection in the ASTRAL-4 trial.

No patients with genotype 2, 4, or 6 HCV infection experienced virologic failure.

Table 13. Study ASTRAL-4: Virologic Outcome for Patients with Genotype 1 and 3 HCV Infection

	EPCLUSA 12 Weeks	EPCLUSA+RBV 12 Weeks	EPCLUSA 24 Weeks
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)
Other[d]	5% (4/82)	2% (2/81)	5% (4/83)

a No patients with genotype 1 HCV had on-treatment virologic failure.
b One patients had on-treatment virologic failure; pharmacokinetic data from this patient was consistent with non-adherence.
c One patients had on-treatment virologic failure.
d Other includes patients who did not achieve SVR and did not meet virologic failure criteria.

Changes in MELD and CPT score from baseline to post-treatment Week 12 were analysed for patients who achieved SVR12 to assess the effect of SVR12 on hepatic function. Of the 82 patients 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 improvements (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; Improvement in CPT score was due to improvements in albumin (increases) and bilirubin (decreases).

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

INDICATIONS

EPCLUSA (sofosbuvir/velpatasvir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection (genotype 1, 2, 3, 4, 5 or 6) in adults.

(see DOSAGE AND ADMINISTRATION section for the recommended regimens for different patient subgroups).

CONTRAINDICATIONS

EPCLUSA tablets are contraindicated in patients with known hypersensitivity to the active substance or to any other component of the tablets.

EPCLUSA is a fixed-dose combination of sofosbuvir and velpatasvir. EPCLUSA should not be administered concurrently with other medicinal products containing any of the same active components.

PRECAUTIONS

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

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

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

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

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

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

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems.

Hepatitis B Virus Reactivation

Cases of Hepatitis B virus (HBV) reactivation, including fatal cases, have been reported during and after treatment of HCV with direct-acting antiviral agents in HCV/HBV co-infected patients. Screening for current or past HBV infection, including testing for HBV surface antigen (HBsAg) and HBV core antibody (anti-HBc), should be performed in all patients before initiation of treatment with EPCLUSA.

Patients with serologic evidence of current or past HBV infection should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation. Consider initiation of HBV antiviral therapy, if indicated.

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

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

Effects on Fertility

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

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

Use in Pregnancy

EPCLUSA (Pregnancy Category B1)

There are no adequate and well-controlled studies with EPCLUSA in pregnant women.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the administration of sofosbuvir or velpatasvir.

Sofosbuvir: No effect on fetal development has been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 was approximately 2- to 5-fold and 6- to 14-fold the exposure in humans at the recommended clinical dose, respectively. Sofosbuvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 6-fold higher than the human exposure at the recommended clinical dose.

Velpatasvir: No effects on fetal development have been observed in mice, rats and rabbits at the highest doses tested. In the mouse, rat and rabbit, AUC exposure to velpatasvir was approximately 31-, 6-, and 0.7-fold, respectively, the exposure in humans at the recommended clinical dose. Velpatasvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 5-fold higher, respectively than the human exposure at the recommended clinical dose.

Because animal reproduction studies are not always predictive of human response, EPCLUSA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ribavirin (Pregnancy Category X)

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. When EPCLUSA is used in combination with ribavirin extreme

care must be taken to avoid pregnancy in female patients and in female partners of male patients. Women of childbearing potential and their male partners must use effective contraception during treatment and for approximately six months after the treatment has concluded as recommended in the product information for ribavirin. If ribavirin is co-administered with EPCLUSA, the contraindications regarding use of ribavirin apply (refer to ribavirin product information).

Use in Lactation

It is not known whether sofosbuvir or velpatasvir or their metabolites are present in human breast milk.

The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups. Velpatasvir was present in the milk of lactating rats, without clear effects on nursing pups. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EPCLUSA and any potential adverse effects on the breastfed infant from EPCLUSA or from the underlying maternal condition.

Paediatric Use

Safety and effectiveness of EPCLUSA in children less than 18 years of age have not been established.

Use in the Elderly

Clinical studies of EPCLUSA included 156 patients aged 65 and over (12% of total number of patients in the Phase 3 clinical trials). No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Genotoxicity

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

Velapatasvir 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

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 200 mg/kg/day in male mice and 600 mg/kg/day in female mice, and 750 mg/kg/day in rats. Exposure to GS-331007 in these studies in mice was up to 3 x (male) and 15 x (female), and in rats up to 7 x (male) and 9 x (female) higher than the clinical exposure at 400 mg sofosbuvir.

Carcinogenicity studies of velpatasvir in mice and rats are ongoing.

INTERACTIONS WITH OTHER MEDICINES

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

Potential for EPCLUSA to Affect Other Drugs

Velpatasvir is an inhibitor of drug transporter P-gp, 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.

Potential for Other Drugs to Affect EPCLUSA

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

Drugs that are potent inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir leading to reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended (see *Precautions*: *Use with Potent Inducers of P-gp and/or Moderate to Potent Inducers of CYP*). 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.

Established and Other Potentially Significant Drug Interactions

Table 14 provides a listing of established or potentially clinically significant drug interations. 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 interations that may occur with EPCLUSA. This table is not all inclusive (see *Pharmacokinetics: Assessment of Drug Interactions*).

Table 14. 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 (e.g., famotidine)[c]		H_2-receptor antagonists may be administered simultaneously with or staggered from EPCLUSA at a dose that does not exceed doses

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
		comparable with famotidine 40 mg twice daily.
Proton-pump inhibitors (e.g., omeprazole)[c]		Proton-pump inhibitor doses comparable with omeprazole 20 mg 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 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 *Precautions: Symptomatic Bradycardia When Coadministered with Amiodarone*).
digoxin[c]	- digoxin	Coadministration of EPCLUSA with digoxin may increase the concentration of digoxin. 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.
tenofovir disoproxil fumurate (tenofovir DF)[c]	- 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 tenofovir DF-containing product's product information for recommendations on renal monitoring.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Herbal Supplements: St. John's wort	¯ sofosbuvir ¯ velpatasvir	Coadministration of EPCLUSA with St. John's wort is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of EPCLUSA. Coadministration is not recommended.
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.

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 combined with the following drugs (see *Pharmacokinetics: Assessment of Drug Interactions*): atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, ketoconazole, lopinavir/ritonavir, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, or tacrolimus.

Effects on ability to drive and use machines

No studies on the effects of EPCLUSA on the ability to drive and use machines have been performed.

ADVERSE EFFECTS

Clinical Trials

The safety assessment of EPCLUSA is based on pooled Phase 3 clinical trial data (ASTRAL-1, ASTRAL-2, and ASTRAL-3) from patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection (with or without compensated cirrhosis) including:

- 1035 patients who received EPCLUSA for 12 weeks,
- 116 patients who received placebo (PBO) for 12 weeks,
- 132 patients who received sofosbuvir (SOF) + ribavirin (RBV) for 12 weeks,
- 275 patients who received SOF + RBV for 24 weeks

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

No adverse drug reactions specific to EPCLUSA have been identified. In clinical trials, headache, fatigue, nausea, and nasopharyngitis were the most common (incidence ≥10%) treatment emergent adverse events reported in patients treated with 12 weeks of EPCLUSA.

Table 15 lists adverse events observed in at least 5% of patients receiving 12 weeks treatment with EPCLUSA in clinical trials compared to placebo. The majority of adverse events presented in Table 15 occurred at severity of grade 1.

Table 15. Adverse Events (All Grades and without Regard to Causality) Reported in ≥5% of Patients Receiving 12 Weeks of Treatment with EPCLUSA Compared to Placebo

	EPCLUSA 12 weeks (N=1035)	Placebo 12 weeks (N=116)
Headache	29%	28%
Fatigue	21%	20%
Nausea	13%	11%
Nasopharyngitis	12%	10%
Insomnia	8%	9%
Diarrhea	7%	7%
Asthenia	6%	8%
Cough	6%	3%
Back pain	5%	9%
Arthralgia	5%	8%

Patients with Decompensated Cirrhosis

No adverse drug reactions specific to EPCLUSA were identified from one open-label trial (ASTRAL-4) in which patients with Child-Pugh Class B cirrhosis received EPCLUSA for 12 weeks (N=90), EPCLUSA+RBV for 12 weeks (N=87) or EPCLUSA for 24 weeks (N=90). The adverse events observed were consistent with expected clinical sequelae of decompensated liver disease, or the known toxicity profile of ribavirin for patients receiving EPCLUSA in combination with RBV.

Among the 87 patients who were treated with EPCLUSA+RBV for 12 weeks, decreases in haemoglobin to less than 10 mg/dL and 8.5 mg/dL during treatment were experienced by 23% and 7% patients, respectively. Ribavirin was discontinued in 15% of patients treated with EPCLUSA+RBV for 12 weeks due to adverse events.

Post marketing Surveillance

The following possible adverse reactions were identified during postapproval use of sofosbuvir. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders

Symptomatic bradycardia (when amiodarone is coadministered with sofosbuvir in combination with another HCV direct acting antiviral) (see *Precautions: Symptomatic Bradycardia When Sofosbuvir is Coadministered with Amiodarone and Another HCV Direct Acting Antiviral*).

DOSAGE AND ADMINISTRATION

The recommended dose of EPCLUSA is one tablet, taken orally, once daily with or without food.

Table 16 provides the recommended treatment regimen based on patient population.

Table 16. Recommended Treatment Regimen Regardless of HCV Genotype

Patient Population	Recommended Treatment Regimen
Patients without cirrhosis and patients with compensated cirrhosis	EPCLUSA for 12 weeks[a]
Patients with decompensated cirrhosis	EPCLUSA + ribavirin[b] for 12 weeks

a. Addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis.
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 ribavirin product information.

Children and Adolescents up to 18 Years of Age

No data are available on which to make a dose recommendation for children < 18 years of age.

Elderly

No dose adjustment is warranted for elderly patients.

Renal Impairment

No dose adjustment of EPCLUSA is required for patients with mild or moderate renal impairment. The safety and efficacy of EPCLUSA have not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis (see *Pharmacokinetics: Special Populations*).

Hepatic Impairment

No dose adjustment of EPCLUSA is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) (see *Pharmacokinetics: Special Populations*). Safety and efficacy of EPCLUSA have been established in patients with decompensated cirrhosis (see *Adverse Effects and Clinical Trials*).

OVERDOSAGE

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.

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. Haemodialysis can efficiently remove the predominant

circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Haemodialysis is unlikely to result in significant removal of velpatasvir since velpatasvir is highly bound to plasma protein.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

PRESENTATION AND STORAGE CONDITIONS

EPCLUSA is available as a fixed-dose combination tablet. Each tablet contains 100 mg velapatasvir and 400 mg sofosbuvir. EPCLUSA tablets are pink, diamond-shaped, film coated tablets, debossed with "GSI" on one side and "7916" on the other side.

EPCLUSA is supplied in high density polyethylene (HDPE) bottles containing 28 tablets and is closed with a child resistant closure.

EPCLUSA should be stored below 30 °C.

NAME AND ADDRESS OF THE SPONSOR

Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne, Victoria 3004

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

19 December 2016