

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Epclusa 400 mg/100 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg sofosbuvir and 100 mg velpatasvir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, diamond-shaped, film-coated tablet of dimensions 20 mm x 10 mm, debossed on one side with “GSI” and “7916” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Epclusa treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Posology

The recommended dose of Epclusa is one tablet, taken orally, once daily with or without food (see section 5.2).

Table 1: Recommended treatment and duration for all HCV genotypes

Patient population ^a	Treatment and duration
Patients without cirrhosis and patients with compensated cirrhosis	Epclusa for 12 weeks Addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis (see section 5.1.)
Patients with decompensated cirrhosis	Epclusa + ribavirin for 12 weeks

a. Includes patients co-infected with human immunodeficiency virus (HIV) and patients with recurrent HCV post-liver transplant (see section 4.4.).

When used in combination with ribavirin, refer also to the Summary of Product Characteristics of the medicinal product containing ribavirin.

The following dosing is recommended where ribavirin is divided in two daily doses and given with food:

Table 2: Guidance for ribavirin dosing when administered with Epclusa to patients with decompensated cirrhosis

Patient	Ribavirin Dose
Child-Pugh-Turcotte (CPT) Class B cirrhosis pre-transplant	1,000 mg per day for patients < 75 kg and 1,200 mg for those weighing ≥ 75 kg
CPT Class C cirrhosis pre-transplant CPT Class B or C post-transplant	Starting dose of 600 mg, which can be titrated up to a maximum of 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg) if well tolerated. If the starting dose is not well tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels

If ribavirin is used in genotype 3 infected patients with compensated cirrhosis (pre- or post-transplant) the recommended dose of ribavirin is 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg).

For ribavirin dose modifications, refer to the Summary of Product Characteristics of the medicinal product containing ribavirin.

Patients should be instructed that if vomiting occurs within 3 hours of dosing an additional tablet of Epclusa should be taken. If vomiting occurs more than 3 hours after dosing, no further dose of Epclusa is needed (see section 5.1).

If a dose of Epclusa is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose of Epclusa at the usual time. Patients should be instructed not to take a double dose of Epclusa.

Patients who have previously failed therapy with an NS5A-containing regimen
Epclusa + ribavirin for 24 weeks may be considered (see section 4.4).

Elderly

No dose adjustment is warranted for elderly patients (see section 5.2).

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 assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) or end stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

Hepatic impairment

No dose adjustment of Epclusa is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C) (see section 5.2). Safety and efficacy of Epclusa have been assessed in patients with CPT Class B cirrhosis, but not in patients with CPT Class C cirrhosis (see sections 4.4, 4.8 and 5.1).

Paediatric population

The safety and efficacy of Epclusa in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

For oral use.

Patients should be instructed to swallow the tablet whole with or without food (see section 5.2). Due to the bitter taste, it is recommended that the film-coated tablet is not chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Use with potent P-gp and potent CYP inducers

Medicinal products that are potent P-glycoprotein (P-gp) or potent cytochrome P450 (CYP) inducers (rifampicin, rifabutin, St. John's wort [*Hypericum perforatum*], carbamazepine, phenobarbital and phenytoin). Co-administration will significantly decrease sofosbuvir or velpatasvir plasma concentrations and could result in loss of efficacy of Epclusa (see section 4.5).

4.4 Special warnings and precautions for use

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

Severe bradycardia and heart block

Cases of severe bradycardia and heart block have been observed when sofosbuvir used in combination with another direct acting antiviral (DAA), is used with concomitant amiodarone with or without other medicinal products that lower heart rate. The mechanism is not established.

The concomitant use of amiodarone was limited through the clinical development of sofosbuvir plus DAAs. Cases are potentially life threatening, therefore amiodarone should only be used in patients on Epclusa when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

Should concomitant use of amiodarone be considered necessary, it is recommended that patients are closely monitored when initiating Epclusa. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Epclusa.

All patients receiving Epclusa in combination with amiodarone with or without other medicinal products that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Patients who have previously failed therapy with an NS5A-containing regimen

There are no clinical data to support the efficacy of sofosbuvir/velpatasvir for the treatment of patients who have failed treatment with a regimen containing another NS5A inhibitor. However, on the basis of NS5A resistance associated variants (RAVs) typically seen in patients who have failed therapy with other NS5A inhibitor containing regimens, the *in vitro* pharmacology of velpatasvir, and the outcomes of sofosbuvir/velpatasvir treatment in NS5A-naïve patients with baseline NS5A RAVs enrolled into the ASTRAL-studies, treatment with Epclusa + RBV for 24 weeks can be considered for patients who have failed therapy on an NS5A-containing regimen and who are deemed at high risk for clinical disease progression and who do not have alternative treatment options.

Renal impairment

No dose adjustment of Epclusa is required for patients with mild or moderate renal impairment. The safety of Epclusa has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) or ESRD requiring haemodialysis. When Epclusa is used in combination with ribavirin refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance < 50 mL/min (see section 5.2).

Use with moderate P-gp inducers or moderate CYP inducers

Medicinal products that are moderate P-gp or moderate CYP inducers (e.g. oxcarbazepine, modafinil or efavirenz) may decrease sofosbuvir or velpatasvir plasma concentrations leading to reduced therapeutic effect of Epclusa. Co-administration of such medicinal products with Epclusa is not recommended (see section 4.5).

Use with certain HIV antiretroviral regimens

Epclusa has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of Epclusa and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Epclusa with the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving Epclusa concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Refer to tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate Summary of Product Characteristics for recommendations on renal monitoring.

HCV/HBV (hepatitis B virus) co-infection

There are no data on the use of Epclusa in patients with HCV/HBV co-infection. Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV co-infected. HBV levels should be monitored during treatment with Epclusa, and during post-treatment follow-up.

CPT Class C cirrhosis

Safety and efficacy of Epclusa has not been assessed in patients with CPT Class C cirrhosis (see sections 4.8 and 5.1).

Liver transplant patients

The safety and efficacy of Epclusa in the treatment of HCV infection in patients who are post-liver transplant have not been assessed. Treatment with Epclusa in accordance with the recommended posology (see section 4.2) should be guided by an assessment of the potential benefits and risks for the individual patient.

4.5 Interaction with other medicinal products and other forms of interaction

As Epclusa contains sofosbuvir and velpatasvir, any interactions that have been identified with these active substances individually may occur with Epclusa.

Potential for Epclusa to affect other medicinal products

Velpatasvir is an inhibitor of drug transporter P-gp, breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3. Co-administration of Epclusa with medicinal products that are substrates of these transporters may increase the exposure of such medicinal products. See Table 3 for examples of interactions with sensitive substrates of P-gp (digoxin), BCRP (rosuvastatin), and OATP (pravastatin).

Potential for other medicinal products to affect Epclusa

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP. Velpatasvir is also a substrate of drug transporter OATP1B. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8 and CYP3A4 was observed. Medicinal products that are potent inducers of P-gp or potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may decrease plasma concentrations of sofosbuvir or velpatasvir leading to reduced therapeutic effect of sofosbuvir/velpatasvir. The use of such medicinal products with Epclusa is contraindicated (see section 4.3). Medicinal products that are moderate P-gp inducers or moderate CYP inducers (e.g. oxcarbazepine, modafinil or efavirenz) may decrease sofosbuvir or velpatasvir plasma concentration leading to reduced therapeutic effect of Epclusa. Co-administration with such medicinal products is not recommended with Epclusa (see section 4.4). Co-administration with medicinal products that inhibit P-gp or BCRP may increase sofosbuvir or velpatasvir plasma concentrations. Medicinal products that inhibit OATP, CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir. Clinically significant medicinal product

interactions with Eplclusa mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; Eplclusa may be co-administered with P-gp, BCRP, OATP and CYP inhibitors.

Interactions between Eplclusa and other medicinal products

Table 3 provides a listing of established or potentially clinically significant medicinal product interactions (where 90% confidence interval [CI] of the geometric least-squares mean [GLSM] ratio were within “↔”, extended above “↑”, or extended below “↓” the predetermined interaction boundaries). The medicinal product interactions described are based on studies conducted with either sofosbuvir/velpatasvir or velpatasvir and sofosbuvir as individual agents, or are predicted medicinal product interactions that may occur with sofosbuvir/velpatasvir. The table is not all-inclusive.

Table 3: Interactions between Eplclusa and other medicinal products

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Eplclusa
	Active	C _{max}	AUC	C _{min}	
ACID REDUCING AGENTS					
					Velpatasvir solubility decreases as pH increases. Medicinal products that increase gastric pH are expected to decrease the concentration of velpatasvir.
<i>Antacids</i>					
e.g. Aluminium or magnesium hydroxide; calcium carbonate (Increase in gastric pH)	Interaction not studied. <i>Expected.</i> ↔ Sofosbuvir ↓ Velpatasvir				It is recommended to separate antacid and Eplclusa administration by 4 hours.
<i>H₂-receptor antagonists</i>					
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose) ^c	Sofosbuvir	↔	↔		H ₂ -receptor antagonists may be administered simultaneously with or staggered from Eplclusa at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Famotidine dosed simultaneously with Eplclusa ^d	Velpatasvir	↓ 0.80 (0.70, 0.91)	↓ 0.81 (0.71, 0.91)		
Cimetidine ^e Nizatidine ^e Ranitidine ^e					
(Increase in gastric pH)					
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose) ^c	Sofosbuvir	↓ 0.77 (0.68, 0.87)	↓ 0.80 (0.73, 0.88)		
Famotidine dosed 12 hours prior to Eplclusa ^d	Velpatasvir	↔	↔		
(Increase in gastric pH)					

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Epclusa
	Active	C _{max}	AUC	C _{min}	
<i>Proton pump inhibitors</i>					
Omeprazole (20 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose fasted) ^c Omeprazole dosed simultaneously with Epclusa ^d Lansoprazole ^e Rabeprazole ^e Pantoprazole ^e Esomeprazole ^e (Increase in gastric pH)	Sofosbuvir	↓ 0.66 (0.55, 0.78)	↓ 0.71 (0.60, 0.83)		Co-administration with proton pump inhibitors is not recommended. If it is considered necessary to co-administer, then Epclusa should be administered with food and taken 4 hours before proton pump inhibitor at max doses comparable to omeprazole 20 mg.
	Velpatasvir	↓ 0.63 (0.50, 0.78)	↓ 0.64 (0.52, 0.79)		
Omeprazole (20 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose fed) ^c Omeprazole dosed 4 hours after Epclusa ^d (Increase in gastric pH)	Sofosbuvir	↓ 0.79 (0.68, 0.92)	↔		
	Velpatasvir	↓ 0.67 (0.58, 0.78)	↓ 0.74 (0.63, 0.86)		
ANTIARRHYTHMICS					
Amiodarone	Interaction not studied. Effect on amiodarone, velpatasvir, and sofosbuvir concentrations unknown.				Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with Epclusa (see sections 4.4 and 4.8).
Digoxin	Interaction only studied with velpatasvir. <i>Expected:</i> ↔ Sofosbuvir				Co-administration of Epclusa with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Epclusa.
Digoxin (0.25 mg single dose) ^f / velpatasvir (100 mg single dose) (Inhibition of P-gp)	Effect on velpatasvir exposure-not studied <i>Expected:</i> ↔ Velpatasvir <i>Observed:</i> Digoxin				
		↑ 1.9 (1.7, 2.1)	↑ 1.3 (1.1, 1.6)		

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Eplusa
	Active	C _{max}	AUC	C _{min}	
ANTICOAGULANTS					
Dabigatran etexilate (Inhibition of P-gp)	Interaction not studied. <i>Expected:</i> ↑ Dabigatran ↔ Sofosbuvir ↔ Velpatasvir				Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with Eplusa. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.
ANTICONVULSANTS					
Carbamazepine Phenytoin Phenobarbital (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ Velpatasvir				Eplusa is contraindicated with carbamazepine, phenobarbital and phenytoin, potent P-gp and CYP inducers (see section 4.3).
Oxcarbazepine (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Eplusa with oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Eplusa. Co-administration is not recommended (see section 4.4).
ANTIFUNGALS					
Ketoconazole	Interaction only studied with velpatasvir <i>Expected:</i> ↔ Sofosbuvir				No dose adjustment of Eplusa or ketoconazole is required.
Ketoconazole (200 mg twice daily)/ velpatasvir (100 mg single dose) ^d (Inhibition of P-gp and CYPs) Itraconazole Voriconazole Posaconazole Isavuconazole	Effect on ketoconazole exposure not studied. <i>Expected:</i> ↔ Ketoconazole <i>Observed:</i> Velpatasvir				
		↑ 1.3 (1.0, 1.6)	↑ 1.7 (1.4, 2.2)		

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Epclusa
	Active	C _{max}	AUC	C _{min}	
ANTIMYCOBACTERIALS					
Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose) ^d (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. <i>Expected:</i> ↔ Rifampicin				Epclusa is contraindicated with rifampicin, a potent P-gp and CYP inducer (see section 4.3).
	<i>Observed:</i> Sofosbuvir	↓ 0.23 (0.19, 0.29)	↓ 0.28 (0.24, 0.32)		
Rifampicin (600 mg once daily)/ velpatasvir (100 mg single dose) (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. <i>Expected:</i> ↔ Rifampicin				
	<i>Observed:</i> Velpatasvir	↓ 0.29 (0.23, 0.37)	↓ 0.18 (0.15, 0.22)		
Rifabutin Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ Velpatasvir				Epclusa is contraindicated with rifabutin, a potent P-gp and CYP inducer (see section 4.3). Co-administration of Epclusa with rifapentine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Epclusa. Co-administration is not recommended (see section 4.4).
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil fumarate	Epclusa has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and C _{max}) was around 40-80% during co-treatment with Epclusa and tenofovir disoproxil fumarate/emtricitabine as part of various HIV regimens. Patients receiving tenofovir disoproxil fumarate and Epclusa concomitantly should be monitored for adverse reactions associated with tenofovir disoproxil fumarate. Refer to the tenofovir disoproxil fumarate-containing product's Summary of Product Characteristics for recommendations on renal monitoring (see section 4.4).				
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600/ 200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Efavirenz	↔	↔	↔	Co-administration of Epclusa with efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is expected to decrease the concentration of velpatasvir. Co-administration of Epclusa with efavirenz-containing regimens is not recommended (see section 4.4).
	Sofosbuvir	↑ 1.2 (1.1, 1.7)	↔		
	Velpatasvir	↓ 0.53 (0.43,	↓ 0.47 (0.39,	↓ 0.43 (0.36,	

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Epclusa
	Active	C _{max}	AUC	C _{min}	
Emtricitabine/ rilpivirine / tenofovir disoproxil fumarate (200/ 25/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Rilpivirine	↔	↔	↔	No dose adjustment of Epclusa or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS					
Atazanavir boosted with ritonavir (300/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200 / 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Atazanavir	↔	↔	↑ 1.4 (1.2, 1.6)	No dose adjustment of Epclusa, atazanavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔		↑ 1.3 (1.5, 1.4)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↑ 1.6 (1.4, 1.7)	↑ 2.4 (2.2, 2.6)	↑ 4.0 (3.6, 4.5)	
Darunavir boosted with ritonavir (800 / 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Darunavir	↔	↔	↔	No dose adjustment of Epclusa, darunavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.62 (0.54, 0.71)	↓ 0.72 (0.66, 0.80)		
	Velpatasvir	↓ 0.76 (0.65, 0.89)	↔	↔	
Lopinavir boosted with ritonavir (4x200 mg/ 50 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Lopinavir	↔	↔	↔	No dose adjustment of Epclusa, lopinavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.59 (0.49, 0.71)	↓ 0.7 (0.6, 0.8)		
	Velpatasvir	↓ 0.70 (0.59, 0.83)	↔	↑ 1.6 (1.4, 1.9)	

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Epclusa
	Active	C _{max}	AUC	C _{min}	
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400 mg twice daily) ^g + emtricitabine/ tenofovir disoproxil fumarate (200 / 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Raltegravir	↔	↔	↓ 0.79 (0.42, 1.5)	No dose adjustment of Epclusa, raltegravir or emtricitabine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate (150/ 150/ 200/ 10 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Elvitegravir	↔	↔	↔	No dose adjustment of Epclusa or elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate is required.
	Cobicistat	↔	↔	↑ 2.0 (1.7, 2.5)	
	Tenofovir alafenamide	↔	↔		
	Sofosbuvir	↔	↑ 1.4 (1.2, 1.5)		
	Velpatasvir	↑ 1.3 (1.2, 1.5)	↑ 1.5 (1.4, 1.7)	↑ 1.6 (1.4, 1.8)	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (150/ 150/ 200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily) ^{c, d}	Elvitegravir	↔	↔	↔	No dose adjustment of Epclusa or elvitegravir/ cobicistat/emtricitabine/ tenofovir disoproxil fumarate is required.
	Cobicistat	↔	↑ 1.2 (1.2, 1.3)	↑ 1.7 (1.5, 1.9)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↑ 1.4 (1.2, 1.5)	
Dolutegravir (50 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)	Dolutegravir	↔	↔	↔	No dose adjustment of Epclusa or dolutegravir is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HERBAL SUPPLEMENTS					
St. John's wort (Induction of P-gp and CYPs)	Interaction not studied. <i>Expected:</i> ↓ Sofosbuvir ↓ Velpatasvir				Epclusa is contraindicated with St. John's wort a potent P-gp and CYP inducer (see section 4.3).

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Epclusa
	Active	C _{max}	AUC	C _{min}	
HMG-CoA REDUCTASE INHIBITORS					
Rosuvastatin	Interaction only studied with velpatasvir <i>Expected:</i> ↔ Sofosbuvir				Co-administration of Epclusa with rosuvastatin increases the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin, at a dose that does not exceed 10 mg, may be administered with Epclusa.
Rosuvastatin (10 mg single dose)/ velpatasvir (100 mg once daily) ^d	<i>Observed:</i> Rosuvastatin	↑ 2.6 (2.3, 2.9)	↑ 2.7 (2.5, 2.9)		
(Inhibition of OATP1B and BCRP)	Effect on velpatasvir exposure not studied <i>Expected:</i> ↔ Velpatasvir				
Pravastatin	Interaction only studied with velpatasvir <i>Expected:</i> ↔ Sofosbuvir				No dose adjustment of Epclusa or pravastatin is required.
Pravastatin (40 mg single dose)/ velpatasvir (100 mg once daily) ^d	<i>Observed:</i> Pravastatin	↑ 1.3 (1.1, 1.5)	↑ 1.4 (1.2, 1.5)		
(Inhibition of OATP1B)	Effect on velpatasvir exposure not studied <i>Expected:</i> ↔ Velpatasvir				
Other statins	<i>Expected:</i> ↑ Statins				Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with Epclusa, careful monitoring for statin adverse reactions should be undertaken and a reduced dose of statins should be considered if required.

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Epclusa
	Active	C _{max}	AUC	C _{min}	
NARCOTIC ANALGESICS					
Methadone (Methadone maintenance therapy [30 to 130 mg daily])/ sofosbuvir (400 mg once daily) ^d	R-methadone	↔	↔	↔	No dose adjustment of Epclusa or methadone is required.
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.3 (1.0, 1.7)		
Methadone	Interaction only studied with sofosbuvir <i>Expected:</i> ↔ Velpatasvir				
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)/ sofosbuvir (400 mg single dose) ^f	Ciclosporin	↔	↔		No dose adjustment of Epclusa or ciclosporin is required.
	Sofosbuvir	↑ 2.5 (1.9, 3.5)	↑ 4.5 (3.3, 6.3)		
Ciclosporin (600 mg single dose) ^f / velpatasvir (100 mg single dose) ^d	Ciclosporin	↔	↓ 0.88 (0.78, 1.0)		No dose adjustment of Epclusa or ciclosporin is required.
	Velpatasvir	↑ 1.6 (1.2, 2.0)	↑ 2.0 (1.5, 2.7)		
Tacrolimus (5 mg single dose) ^f / sofosbuvir (400 mg single dose) ^d	Tacrolimus	↓ 0.73 (0.59, 0.90)	↑ 1.1 (0.84, 1.4)		No dose adjustment of Epclusa or tacrolimus is required.
	Sofosbuvir	↓ 0.97 (0.65, 1.4)	↑ 1.1 (0.81, 1.6)		
Tacrolimus	Effect on velpatasvir exposure not studied. <i>Expected:</i> ↔ Velpatasvir				

Medicinal product by therapeutic areas/Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval) ^{a,b}				Recommendation concerning co-administration with Epclusa
	Active	C _{max}	AUC	C _{min}	
ORAL CONTRACEPTIVES					
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily) ^d	Norelgestromin	↔	↔	↔	No dose adjustment of oral contraceptives is required.
	Norgestrel	↔	↑ 1.2 (0.98, 1.5)	↑ 1.2 (1.0, 1.5)	
	Ethinyl estradiol	↔	↔	↔	
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ velpatasvir (100 mg once daily) ^d	Norelgestromin	↔	↔	↔	
	Norgestrel	↔	↔	↔	
	Ethinyl estradiol	↑ 1.4 (1.2, 1.7)	↔	↓ 0.83 (0.65, 1.1)	

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00.

b. All interaction studies conducted in healthy volunteers.

c. Administered as Epclusa.

d. Lack of pharmacokinetics interaction bounds 70-143%.

e. These are medicinal products within class where similar interactions could be predicted.

f. Bioequivalence/Equivalence boundary 80-125%.

g. Lack of pharmacokinetics interaction bounds 50-200%.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir, velpatasvir or Epclusa in pregnant women.

Sofosbuvir

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

It has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose (see section 5.3).

Velpatasvir

Animal studies have shown a possible link to reproductive toxicity (see section 5.3).

As a precautionary measure, Epclusa use is not recommended during pregnancy.

Breast-feeding

It is unknown whether sofosbuvir, metabolites of sofosbuvir or velpatasvir are excreted in human milk.

Available pharmacokinetic data in animals have shown excretion of velpatasvir and metabolites of sofosbuvir in milk.

A risk to the newborns/infants cannot be excluded. Therefore, Epclusa should not be used during breast-feeding.

Fertility

No human data on the effect of Epclusa on fertility are available. Animal studies do not indicate harmful effects of sofosbuvir or velpatasvir on fertility.

If ribavirin is co-administered with Epclusa, refer to the Summary of Product Characteristics for ribavirin for detailed recommendations regarding pregnancy, contraception, and breast-feeding.

4.7 Effects on ability to drive and use machines

Epclusa has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety assessment of Epclusa was based on pooled Phase 3 clinical study data from patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection (with or without compensated cirrhosis) including 1,035 patients who received Epclusa for 12 weeks.

The proportion of patients who permanently discontinued treatment due to adverse events was 0.2% and the proportion of patients who experienced any severe adverse events was 3.2% for patients receiving Epclusa for 12 weeks. In clinical studies, headache, fatigue and nausea were the most common (incidence $\geq 10\%$) treatment emergent adverse events reported in patients treated with 12 weeks of Epclusa. These and other adverse events were reported at a similar frequency in placebo treated patients compared with Epclusa treated patients.

Patients with decompensated cirrhosis

The safety profile of Epclusa has been evaluated in one open-label study in which patients with CPT 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 ribavirin.

Among the 87 patients who were treated with Epclusa + RBV for 12 weeks, decreases in haemoglobin to less than 10 g/dL and 8.5 g/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.

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir used in combination with another direct acting antiviral, is used with concomitant amiodarone and/or other medicinal products that lower heart rate (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest documented doses of sofosbuvir and velpatasvir were a single dose of 1,200 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antiviral, 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 analogue triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of sofosbuvir) 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

The 50% effective concentration (EC₅₀) values of sofosbuvir and velpatasvir against full-length or chimeric replicons encoding NS5B and NS5A sequences from the laboratory strains are presented in Table 4. The EC₅₀ values of sofosbuvir and velpatasvir against clinical isolates are presented in Table 5.

Table 4: 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 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 5: 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.

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 the 50% inhibitory concentration (IC₅₀).

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 studies

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 three Phase 3 studies, 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, one 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 2 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 one Phase 3 study in patients with decompensated cirrhosis who received Epclusa + 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 to treatment.

In this study, 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 in three Phase 3 clinical studies (ASTRAL-1, ASTRAL-2 and ASTRAL-3). Of the 1,035 patients treated with sofosbuvir/velpatasvir in the three Phase 3 clinical studies, 1,023 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 studies, 380/1,023 (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.

Baseline RAVs had no relevant impact on SVR12 rates in patients infected with genotype 1, 2, 4, 5 and 6 HCV, as summarised in Table 6. Genotype 3 infected patients with the NS5A RAV Y93H at baseline had a lower SVR12 rate than patients without Y93H after treatment with Epclusa for 12 weeks, as summarised in Table 7. In the ASTRAL-3 study, the Y93H RAV was detected at baseline in 9% of patients treated with Epclusa.

Table 6: SVR12 in patients with or without baseline NS5A RAVs by HCV genotype (studies ASTRAL-1, ASTRAL-2 and ASTRAL-3)

	Epclusa 12 weeks			
	Genotype 1	Genotype 3	Genotypes 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)

Table 7: SVR12 in patients with and without baseline Y93H, 1% Cut-off (Resistance Analysis Population Set) ASTRAL 3

	Epclusa 12 Weeks		
	All Subjects (n=274)	Cirrhotic (n=80)	Non-Cirrhotic (n=197)
Overall	95.3% (263/274)	91.3% (73/80)	97.9% (190/194)
95% CI	92.9% to 98.0%	82.8% to 96.4%	92.8% to 98.6%
SVR with Y93H	84.0% (21/25)	50.0% (2/4)	90.5% (19/21)
95% CI	63.9% to 95.5%	6.8% to 93.2%	69.6% to 98.8%
SVR without Y93H	96.4% (242/249)	93.4% (71/76)	98.8% (171/173)
95% CI	94.3% to 98.9%	85.3% to 97.8%	95.9% to 99.9%

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 studies. 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 (CPT Class B)

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients with decompensated cirrhosis in one Phase 3 study (ASTRAL-4). Of the 87 patients treated with Epclusa + RBV, 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 for this study is shown in Table 8.

Table 8: SVR12 in patients with or without baseline NS5A RAVs by HCV genotype (study ASTRAL-4)

	Epclusa + RBV 12 weeks			
	Genotype 1	Genotype 3	Genotypes 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 to treatment.

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 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 assessed in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Clinical efficacy and safety

The efficacy of Epclusa was evaluated in three Phase 3 studies in patients with genotype 1 to 6 HCV infection with or without compensated cirrhosis and one Phase 3 study in patients with genotype 1 to 6 HCV infection with decompensated cirrhosis, as summarised in Table 9.

Table 9: Studies conducted with Epclusa in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection

Study	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)

The ribavirin 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 studies or in combination with Epclusa in the ASTRAL-4 study. Ribavirin dose adjustments were performed according to the ribavirin prescribing information. Serum HCV RNA values were measured during the clinical studies using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL. Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint 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 (study 1138)

ASTRAL-1 was a randomised, double-blind, placebo-controlled study 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 of at least 30 kg/m²; 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 of at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced.

Table 10 presents the SVR12 for the ASTRAL-1 study by HCV genotypes. No patients in the placebo group achieved SVR12.

Table 10: SVR12 in study ASTRAL-1 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 SVR12								
On-treatment virologic failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse ^a	< 1% (2/623)	< 1% (1/209)	1% (1/118)	1% (2/327)	0/104	0/116	0/35	0/41
Other ^b	1% (4/624)	1% (3/210)	0/118	1% (3/328)	0/104	0/116	3% (1/35)	0/41

GT = genotype

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 SVR12 and did not meet virologic failure criteria.

Genotype 2 HCV-infected adults – ASTRAL-2 (study 1139)

ASTRAL-2 was a randomised, open-label study 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 *versus* 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 of at least 30 kg/m²; 62% had non-CC IL28B alleles (CT or TT); 80% had baseline HCV RNA levels of at least 800,000 IU/mL; 14% had compensated cirrhosis and 15% were treatment-experienced.

Table 11 presents the SVR12 for the ASTRAL-2 study.

Table 11: SVR12 in study ASTRAL-2 (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 SVR12		
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 SVR12 and did not meet virologic failure criteria.

Treatment with Epclusa for 12 weeks demonstrated the statistical superiority (p = 0.018) over 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 (study 1140)

ASTRAL-3 was a randomised, open-label study 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 *versus* treatment-experienced).

Demographics and baseline characteristics were balanced across the two 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; 1% were Black; 20% had a baseline body mass index of at least 30 kg/m²; 61% had non-CC IL28B alleles (CT or TT); 70% had baseline HCV RNA levels of at least 800,000 IU/mL, 30% had compensated cirrhosis and 26% were treatment-experienced.

Table 12 presents the SVR12 for the ASTRAL-3 study.

Table 12: SVR12 in study ASTRAL-3 (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 SVR12		
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 SVR12 and did not meet virologic failure criteria.

Treatment with Epclusa for 12 weeks demonstrated the 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 13.

Table 13: SVR12 for selected subgroups in study ASTRAL-3 (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)
SVR12				
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 (study 1137)

ASTRAL-4 was a randomised, open-label study in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection and CPT Class 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 of at least 30 kg/m². 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% of the patients had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels of at least 800,000 IU/mL, 55% were treatment-experienced; 90% and 95% of patients had CPT Class B cirrhosis and Model for End Stage Liver Disease (MELD) score ≤ 15 at baseline, respectively.

Table 14 presents the SVR12 for the ASTRAL-4 study by HCV genotype.

Table 14: SVR12 in study ASTRAL-4 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 15 presents the virologic outcome for patients with genotype 1 or 3 HCV infection in the ASTRAL-4 study.

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

Table 15: Virologic outcome for patients with genotype 1 and 3 HCV infection in study ASTRAL-4

	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 patient had on-treatment virologic failure; pharmacokinetic data from this patient was consistent with non-adherence to treatment.

c. One patient had on-treatment virologic failure.

d. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Changes in the parameters found in the CPT score system in patients achieving SVR12 in ASTRAL-4 (all 3 regimens) are shown in Table 16.

Table 16: Changes in CPT score parameters from baseline to week 12 and 24 post-treatment in patients achieving SVR12, ASTRAL-4

	Albumin	Bilirubin	INR	Ascites	Encephalopathy
Post-treatment Week 12 (N=236), % (n/N)					
Decreased score (Improvement)	34.5% (79/229)	17.9% (41/229)	2.2% (5/229)	7.9% (18/229)	5.2% (12/229)
No change	60.3% (138/229)	76.4% (175/229)	96.5% (221/229)	89.1% (204/229)	91.3% (209/229)
Increased score (Worsening)	5.2% (12/229)	5.7% (13/229)	1.3% (3/229)	3.1% (7/229)	3.5% (8/229)
No assessment	7	7	7	7	7
Post-treatment Week 24 (N=236), % (n/N)					
Decreased score (Improvement)	39.4% (84/213)	16.4% (35/213)	2.3% (5/213)	15.0% (32/213)	9.4% (20/213)
No change	54.0% (115/213)	80.8% (172/213)	94.8% (202/213)	81.2% (173/213)	88.3% (188/213)
Increased score (Worsening)	6.6% (14/213)	2.8% (6/213)	2.8% (6/213)	3.8% (8/213)	2.3% (5/213)
No assessment	23	23	23	23	23

Note: Baseline frequency of ascites was: 20% none, 77% mild/moderate, 3% severe
Baseline frequency of encephalopathy was: 38% none, 62% grade 1-2.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Epclusa in one or more subsets of the paediatric population in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

Elderly

Clinical studies of Epclusa included 156 patients aged 65 and over (12% of total number of patients in the Phase 3 clinical studies). The response rates observed for patients ≥ 65 years of age were similar to that of patients < 65 years of age, across treatment groups.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic properties of sofosbuvir, GS-331007 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 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed 3 hours post-dose. Velpatasvir median peak concentrations were observed at 3 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 = 1,428) and velpatasvir (n = 1,425) were 1,260, 13,970 and 2,970 ng•h/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.

Effects 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 resulted in a 34% and 21% increase in velpatasvir AUC_{0-inf} , respectively, and a 31% and 5% increase in velpatasvir C_{max} , respectively. The

moderate or high fat meal increased sofosbuvir AUC_{0-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-inf} , but resulted in a 25% and 37% decrease in its C_{max} , respectively. The response rates in Phase 3 studies 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 $\mu\text{g/mL}$ to 20 $\mu\text{g/mL}$. 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 $\mu\text{g/mL}$ to 1.8 $\mu\text{g/mL}$. 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.

Biotransformation

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*. Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes. 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. The monohydroxylated and desmethylated velpatasvir were the metabolites identified in human plasma. Unchanged velpatasvir is the major species present in faeces.

Elimination

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 a major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of Epclusa was approximately 15 hours.

Linearity/non-linearity

Velpatasvir AUC increases in a nearly dose proportional manner over the dose range of 25 mg to 150 mg. Sofosbuvir and GS-331007 AUCs are near dose-proportional over the dose range of 200 mg to 1,200 mg.

In vitro potential for sofosbuvir/velpatasvir drug-drug interactions

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Velpatasvir is also a substrate of OATP1B. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

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 plasma concentration, velpatasvir is not an inhibitor of hepatic transporters bile salt export pump (BSEP), sodium taurocholate cotransporter protein (NTCP), OATP2B1, OATP1A2 or organic cation transporter (OCT) 1, renal transporters OCT2, OAT1, OAT3, multidrug resistance-associated protein 2 (MRP2) or multidrug and toxin extrusion protein (MATE) 1, or CYP or uridine glucuronosyltransferase (UGT) 1A1 enzymes.

Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1. GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Pharmacokinetics in special populations

Race and gender

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

Elderly

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.

Renal impairment

The pharmacokinetics of sofosbuvir was studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73 m²), moderate (eGFR ≥ 30 and < 50 mL/min/1.73 m²), severe renal impairment (eGFR < 30 mL/min/1.73 m²) and patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73 m²), the sofosbuvir AUC_{0-inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88% and 451% higher, respectively. In patients with ESRD, sofosbuvir AUC_{0-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-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 (see section 4.2).

The pharmacokinetics of velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Relative to subjects with normal renal function, velpatasvir AUC_{inf} was 50% higher in subjects with severe renal impairment (see section 4.2).

Hepatic impairment

The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (CPT Class B and C). Relative to patients with normal hepatic function, the sofosbuvir AUC₀₋₂₄ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC₀₋₂₄ 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 to sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative patients with moderate and severe hepatic impairment (CPT Class B and C). Compared to subjects with normal hepatic function velpatasvir total plasma exposure (AUC_{inf}) was similar in patients with moderate or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to velpatasvir (see section 4.2).

Body weight

Body weight did not have a clinically significant effect on sofosbuvir or velpatasvir exposure according to a population pharmacokinetic analysis.

Paediatric population

The pharmacokinetics of sofosbuvir, GS-331007 and velpatasvir in paediatric patients have not been established (see section 4.2).

5.3 Preclinical safety data

Sofosbuvir

Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity and exposure to the major metabolite GS-331007 was instead used to estimate exposure margins.

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. No teratogenic effects were observed in the rat and rabbit developmental toxicity studies with sofosbuvir. Sofosbuvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study.

Sofosbuvir was not a carcinogen in the 2-year mouse and rat carcinogenicity studies at GS-331007 exposures up to 15 and 9 times, respectively, higher than human exposure.

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.

Velpatasvir had no adverse effects on mating and fertility. No teratogenic effects were observed in the mouse and rat developmental toxicity studies with velpatasvir at AUC exposures approximately 31- and 6--fold higher, respectively, than the human exposure at the recommended clinical dose. However, a possible teratogenic effect was indicated in rabbits where an increase in total visceral malformations was seen in exposed animals at AUC exposures up to 0.7 fold the human exposure at recommended clinical dose. The human relevance of this finding is not known. 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 than the human exposure at the recommended clinical dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Copovidone
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film-coating

Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Eplclusa tablets are supplied in high density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 28 film-coated tablets with polyester coil.

The following pack sizes are available: outer cartons containing 1 bottle of 28 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd.
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1116/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
IRELAND

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Epclusa 400 mg/100 mg film-coated tablets
sofosbuvir/velpatasvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg sofosbuvir and 100 mg velpatasvir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd.
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1116/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Epclusa [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Epclusa 400 mg/100 mg film-coated tablets sofosbuvir/velpatasvir

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Epclusa is and what it is used for
2. What you need to know before you take Epclusa
3. How to take Epclusa
4. Possible side effects
5. How to store Epclusa
6. Contents of the pack and other information

1. What Epclusa is and what it is used for

Epclusa is a medicine that contains the active substances sofosbuvir and velpatasvir in a single tablet. It is given to treat a chronic (long-term) viral infection of the liver called hepatitis C in adults of 18 years and older.

The active substances in this medicine work together by blocking two different proteins that the virus needs to grow and reproduce itself, allowing the infection to be permanently eliminated from the body.

Epclusa is sometimes taken with another medicine, ribavirin.

It is very important that you also read the leaflets for the other medicines that you will be taking with Epclusa. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take Epclusa

Do not take Epclusa

- **If you are allergic** to sofosbuvir, velpatasvir or any of the other ingredients of this medicine (listed in section 6 of this leaflet).

→ If this applies to you, **do not take Epclusa and tell your doctor immediately.**

- **If you are currently taking any of the following medicines:**
 - **rifampicin** and **rifabutin** (antibiotics used to treat infections, including tuberculosis);
 - **St. John's wort** (*Hypericum perforatum* – herbal medicine used to treat depression);
 - **carbamazepine, phenobarbital** and **phenytoin** (medicines used to treat epilepsy and prevent seizures);

Warnings and precautions

Talk to your doctor if you:

- **have liver problems** other than from hepatitis C, for instance
 - **if you have hepatitis B**, since your doctor may want to monitor you more closely;
 - **if you have had a liver transplant**
- **have kidney problems**, since Epclusa has not been fully tested in patients with some severe kidney problems;
- **are taking treatment for human immunodeficiency virus (HIV) infection**, since your doctor may want to monitor you more closely.

Talk to your doctor or pharmacist before taking Epclusa if:

- you currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats (your doctor may consider alternative treatments if you have taken this medicine).

Tell your doctor immediately if you are taking any medicines for heart problems and during treatment you experience:

- shortness of breath
- light-headedness
- palpitations
- fainting

Blood tests

Your doctor will test your blood before, during and after your treatment with Epclusa. This is so that:

- Your doctor can decide if you should take Epclusa and for how long;
- Your doctor can confirm that your treatment has worked and you are free of the hepatitis C virus.

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age. The use of Epclusa in children and adolescents has not yet been studied.

Other medicines and Epclusa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. If you are not sure talk to your doctor or pharmacist.

Some medicines should not be taken with Epclusa.

- **Do not take any other medicine that contains sofosbuvir, one of the active substances in Epclusa.**

Tell your doctor or pharmacist if you are taking any of the medicines below:

- **amiodarone** used to treat irregular heartbeats;
- **rifapentine** (antibiotic used to treat infections, including tuberculosis);
- **oxcarbazepine** (medicine used to treat epilepsy and prevent seizures)
- **tenofovir disoproxil fumarate** or any medicine containing tenofovir disoproxil fumarate, used to treat HIV infection;
- **efavirenz** used to treat HIV infection;
- **digoxin** used to treat heart conditions;
- **dabigatran** used to thin the blood;
- **modafinil** used to treat sleep disorders;
- **rosuvastatin** or **other statins** used to treat high cholesterol.

Taking Epclusa with any of these may stop your medicines from working properly, or make any side effects worse. Your doctor may need to give you a different medicine or adjust the dose of medicine you are taking. This change could be to Epclusa or another medicine you are taking.

- **Get advice from a doctor or pharmacist** if you take medicines used to treat **stomach ulcers, heartburn or acid reflux** as they can decrease the amount of velpatasvir in your blood. These medicines include:
 - antacids (such as aluminium/magnesium hydroxide or calcium carbonate). These should be taken at least 4 hours before or 4 hours after Epclusa;
 - proton pump inhibitors (such as omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole). Epclusa should be taken with food when using a proton pump inhibitor.
 - H₂-receptor antagonists (such as famotidine, cimetidine, nizatidine or ranitidine). If you need high doses of these medicines your doctor may give you a different medicine instead or adjust the dose of the medicine you are taking.

These medicines can decrease the amount of velpatasvir in your blood. If you are taking one of these medicines your doctor will either give you a different medicine for stomach ulcers, heartburn or acid reflux, or recommend how and when you take that medicine.

Pregnancy and contraception

The effects of Epclusa during pregnancy are not known. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Epclusa is sometimes used together with ribavirin. Ribavirin can harm your unborn baby. It is therefore very important that you (or your partner) do not become pregnant during this treatment or for a period of time after completing treatment. You must read the “Pregnancy” section in the ribavirin package leaflet very carefully. Ask your doctor for effective contraception method suitable for you and your partner.

Breast-feeding

Do not breast-feed during treatment with Epclusa. It is not known whether sofosbuvir or velpatasvir, the two active substances of Epclusa, pass into human breast milk.

Driving and using machines

Epclusa should not affect your ability to drive or use any tools or machinery.

3. How to take Epclusa

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose

The recommended dose is **one tablet once a day for 12 weeks**.

Swallow the tablet whole with or without food. Do not chew, crush or split the tablet as it has a very bitter taste.

If you are taking an antacid, take it at least 4 hours before or at least 4 hours after Epclusa.

If you are taking a proton pump inhibitor, take Epclusa with food.

If you are sick (vomit) after taking Epclusa it may affect the amount of Epclusa in your blood. This may make Epclusa work less well.

- If you are sick (vomit) **less than 3 hours after** taking Epclusa, take another tablet.
- If you are sick (vomit) **more than 3 hours after** taking Epclusa, you do not need to take another tablet until your next scheduled tablet.

If you take more Epclusa than you should

If you accidentally take more than the recommended dose you should contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Epclusa

It is important not to miss a dose of this medicine.

If you do miss a dose, work out how long it is since you last took your Epclusa:

- **If you notice within 18 hours** of the time you usually take Epclusa, you must take the tablet as soon as possible. Then take the next dose at your usual time.
- **If it's 18 hours or more** after the time you usually take Epclusa, wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

Do not stop taking Epclusa

Do not stop taking this medicine unless your doctor tells you to. It is very important that you complete the full course of treatment to give the medicine the best chance to treat your hepatitis C virus infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine may cause side effects, although not everybody gets them.

→**If you get any side effects tell your doctor.**

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epclusa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Epclusa contains

- **The active substances are** sofosbuvir and velpatasvir. Each film-coated tablet contains 400 mg sofosbuvir and 100 mg velpatasvir.

- **The other ingredients are**

Tablet core:

Copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Film-coating:

Polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red

What Epclusa looks like and contents of the pack

The film-coated tablets are pink, diamond-shaped tablets debossed with “GSI” on one side and “7916” on the other side. The tablet is 20 mm long and 10 mm wide.

The following pack sizes are available:

- outer cartons containing 1 bottle of 28 film-coated tablets

Marketing Authorisation Holder

Gilead Sciences International Ltd.
Cambridge
CB21 6GT
United Kingdom

Manufacturer

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.