APPROVED PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

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.

Red, diamond-shaped, film-coated tablets, 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 infection irrespective of genotype in treatment naïve or treatment experienced patients aged 12 years and older and weighing at least 30 kg

- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis in combination with ribavirin (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology and method of administration

The recommended dose of Epclusa in adults is one 400 mg/100 mg tablet, taken orally, once daily with or without food (see section 5.2).

The recommended dose of Epclusa in patients aged 12 to < 18 years and weighing at least 30 kg is one 400 mg/100 mg tablet, taken orally, once daily with or without food (see section 5.2).

Table 1: Recommended treatment and duration for adults regardless of HCV genotypes

Adult patient population	Treatment and duration
Patients without cirrhosis and patients with compensated cirrhosis	Epclusa for 12 weeks No evidence that addition of ribavirin to Epclusa in patients with compensated cirrhosis will improve outcome.
Patients with decompensated cirrhosis	Epclusa + ribavirin[a] for 12 weeks

When used in combination with ribavirin, refer also to the PI of ribavirin.
The following dosing is recommended for adults where ribavirin is divided in two daily doses and given with food.

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

Adult patient	Ribavirin dose
Child-Pugh-Turcotte (CPT) Class B cirrhosis	1,000 mg per day for patients < 75 kg and 1,200 mg for those weighing ≥ 75 kg
Safety and efficacy of Epclusa have not been established in patients with	

Child Pugh C decompensated cirrhosis The safety and efficacy of Epclusa have not been established in CPT Class B or C post-transplant patients	

For ribavirin dose modifications, refer to the ribavirin PI.

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

If a dose 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 at the usual time. Patients should be instructed not to take a double dose.

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 renal impairment, including end stage renal disease (ESRD) requiring dialysis (see section 5.2).

Hepatic Impairment

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

Paediatric population

The safety and efficacy of Epclusa in children aged less than 12 years and weighing less than 30 kg have not yet been established.

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.

Pregnancy and lactation with or without the use of ribavirin

Concomitant use with moderate to strong P-glycoprotein (P-gp) inducers and moderate to strong CYP inducers

Concomitant use with medicines that are strong P-glycoprotein (P-gp) or strong cytochrome P450 (CYP) inducers (rifampicin, rifabutin, St. John's wort [Hypericum perforatum], carbamazepine, phenobarbital and phenytoin) will significantly decrease sofosbuvir and/or velpatasvir plasma concentrations and could result in loss of efficacy of Epclusa (see section 4.5). Medicines that are moderate P-gp inducers or moderate CYP inducers include rifapentine, oxcarbazepine, modafinil and efavirenz may decrease sofosbuvir and/or velpatasvir concentrations that could result in loss of efficacy of Epclusa.

If Epclusa is used in combination with ribavirin the contraindications of ribavirin must be adhered to.

4.4 Special warnings and precautions for use

EPCLUSA should not be administered concomitantly with other medicines containing sofosbuvir

Severe bradycardia and heart block

Severe and potentially life-threatening bradycardia and heart block have been observed when sofosbuvir-containing regimens such as Epclusa are used in combination with amiodarone with or without other medicines that lower heart rate. The mechanism is not established.

Amiodarone should only be used in patients on Epclusa when other alternative anti-dysrhythmic 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 brady-dysrhythmia should be continuously monitored for 48 hours in an appropriate in-patient (hospital) setting after which outpatient or self-monitoring of heart rate should be done daily for at least the first two weeks of treatment.

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 medicines 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.

Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct acting antiviral medicines including Epclusa. HBV screening should be performed in all patients before initiation of treatment. Treatment with Epclusa should not be initiated in patients who screened positive for Hepatitis B virus infection. The safety and efficacy of Epclusa have not been established in HCV patients co-infected with Hepatitis B virus infection (HBV). HCV/HBV coinfected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Use with ribavirin

When Epclusa is used in combination with ribavirin refer also to the **Professional information** for ribavirin for patients with creatinine clearance < 50 ml/min (see section 5.2).

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 the PIs

of tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate for recommendations on renal monitoring.

Use in diabetic patients

Hyperglycaemia and/or hypoglycaemia have been reported with Epclusa treatment. The medical practitioner should inform patients on the possibility of blood glucose changes during treatment with Epclusa before initiating treatment. Glucose levels of diabetic patients initiating Epclusa should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when Epclusa is initiated.

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.

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 Medicines

Velpatasvir is an inhibitor of drug transporter P-gp, breast cancer resistance protein (BCRP), (OATP)1B1 and OATP1B3. Coadministration of EPCLUSA with medicines that are substrates of these transporters may increase the exposure of such medicines.

See Table 3 for examples of interactions with sensitive substrates of P-gp (digoxin), BCRP (rosuvastatin), and OATP (pravastatin).

Potential for other medicines 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.

Medicines that are strong inducers of P-gp and/or strong inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. carbamazepine, phenobarbital and phenytoin rifampicin, rifabutin and St. John’s wort,) have been shown to decrease plasma concentrations of sofosbuvir and/or velpatasvir leading to reduced therapeutic effect of EPCLUSA. The use of such medicines with EPCLUSA is contraindicated (see section 4.3).

Medicines 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 medicines is not recommended with Epclusa. (see section 4.4)

Coadministration with medicines that inhibit P-gp and/or BCRP may increase sofosbuvir and/or velpatasvir plasma concentrations.
Medicines that inhibit OATP, CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir. Clinically significant interactions with Epclusa mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; EPCLUSA may be co-administered with P-gp, BCRP, OATP and CYP inhibitors.

Patients treated with vitamin K antagonists

As liver function may change during treatment with Epclusa, frequent monitoring of the International Normalised Ratio (INR) is required in patients on treatment with Vitamin K antagonists (e.g. Warfarin).

Impact of DAA therapy on drugs metabolized by the liver

The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

Interactions between Epclusa and other medicines

Table 3 provides a listing of established or potentially clinically significant medicine 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 interactions described are based on studies conducted with either sofosbuvir/velpatasvir or velpatasvir and sofosbuvir as individual medicines, or are predicted medicine interactions that may occur with sofosbuvir/velpatasvir. The table is not all-inclusive.

Table 3: Interactions between Epclusa and other medicines

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ACID REDUCING AGENTS					
					Velpatasvir solubility decreases as pH increases. Medicines that increase gastric pH are expected to decrease the concentration of velpatasvir.
Antacids					
e.g. Aluminium or magnesium hydroxide; calcium carbonate (Increase in gastric pH)	Interaction not studied. *Expected.* ↔ Sofosbuvir ↓ Velpatasvir				It is recommended to separate antacid and Epclusa administration by 4 hours.
H_2-receptor antagonists					
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose)[c] Famotidine dosed simultaneously with Epclusa[d] Cimetidine[e] Nizatidine[e] Ranitidine[e] (Increase in gastric pH)	Sofosbuvir	↔	↔		H_2-receptor antagonists may be administered simultaneously with or staggered from Epclusa at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
	Velpatasvir	↓ 0,80 (0,70 , 0,91)	↓ 0,81 (0,71 , 0,91)		

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose)[c] Famotidine dosed 12 hours prior to Epclusa[d] (Increase in gastric pH)	Sofosbuvir	↓ 0,77 (0,68, 0,87)	↓ 0,80 (0,73, 0,88)		
	Velpatasvir	↔	↔		
Proton pump inhibitors					
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)		
ANTIDYSRHYTHMICS					

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
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 medicine is administered with Epclusa (see sections 4.4 and 4.8).
Digoxin	Interaction only studied with velpatasvir. *Expected:* ↔ 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 *Expected:* ↔ Velpatasvir				
	Observed: Digoxin	↑ 1,9 (1,7, 2,1)	↑ 1,3 (1,1, 1,6)		

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ANTICOAGULANTS					
Dabigatran etexilate (Inhibition of P-gp)	Interaction not studied. *Expected:* ↑ Dabigatran ↔ Sofosbuvir ↔ Velpatasvir				Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with Epclusa. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.
Vitamin K antagonists	Interaction not studied				Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Epclusa.
ANTICONVULSANTS					
Phenytoin Phenobarbital (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Epclusa is contraindicated with phenobarbital and phenytoin, potent P-gp and CYP inducers (see section 4.3).

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Carbamazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir				Epclusa is contraindicated with carbamazepine (see section 4.3).
	Observed: Sofosbuvir	↓0,52 (0,43 , 0,62)	↓ 0,52 (0,46 , 0,59)		
Oxcarbazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Epclusa with oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Epclusa. Co-administration is contraindicated.

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ANTIFUNGALS					
Ketoconazole	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Epclusa or ketoconazole is required.
Ketoconazole (200 mg twice daily)/ velpatasvir (100 mg single dose)[d] (Inhibition of P-gp and CYPs) Itraconazole[e] Voriconazole[e] Posaconazole[e] Isavuconazole[e]	Effect on ketoconazole exposure not studied. *Expected:* ↔ Ketoconazole				
	Observed: Velpatasvir	↑ 1,3 (1,0, 1,6)	↑ 1,7 (1,4, 2,2)		
ANTIMYCOBACTERIALS					
Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d] (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				Epclusa is contraindicated with rifampicin, (see section 4.3).
	Observed: 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. *Expected:* ↔ Rifampicin				
	Observed: Velpatasvir	↓ 0,29 (0,23 , 0,37)	↓ 0,18 (0,15 , 0,22)		

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Rifabutin (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir				Epclusa is contraindicated with rifabutin, (see section 4.3).
	Observed: Sofosbuvir	↓ 0,64 (0,.53, 0,77)	↓ 0,76 (0,63, 0,91)		
Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				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 contraindicated.
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 should not receive tenofovir disoproxil fumarate and Epclusa concomitantly.				

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
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 contraindicated.
	Sofosbuvir	↑ 1,4 (1,1, 1,7)	↔		
	Velpatasvir	↓ 0,53 (0,43, 0,64)	↓ 0,47 (0,39, 0,57)	↓ 0,43 (0,36, 0,52)	
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)	

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
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)	
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	↔	↔	↔	

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
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	↔	↔	↑ 1,7 (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. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Epclusa is contraindicated with St. John's wort a potent P-gp and CYP inducer (see section 4.3).

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
HMG-CoA REDUCTASE INHIBITORS					
Atorvastatin (40 mg single dose) + sofosbuvir / velpatasvir (400/ 100 mg once daily)[d]	*Observed:* Atorvastatin	↑ 1,7 (1,5, 1,9)	↑ 1,5 (1,5, 1,6)		No dose adjustment of Epclusa or atorvastatin is required.
Rosuvastatin	Interaction only studied with velpatasvir *Expected:* ↔ 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 (see section 4.4).
Rosuvastatin (10 mg single dose)/ velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B and BCRP)	*Observed:* Rosuvastatin	↑ 2,6 (2,3, 2,9)	↑ 2,7 (2,5, 2,9)		
	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
Pravastatin	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Epclusa or pravastatin is required.
Pravastatin (40 mg single dose)/ velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B)	*Observed:* Pravastatin	↑ 1,3 (1,1, 1,5)	↑ 1,4 (1,2, 1,5)		
	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
Other statins	*Expected:* ↑ 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.
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 *Expected:* ↔ Velpatasvir				

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine levels. Mean ratio (90 % confidence interval)[a,b]**				**Recommendation concerning co-administration with Epclusa**
	Active	**C_{max}**	**AUC**	**C_{min}**	
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)/ sofosbuvir (400 mg single dose)[f]	Ciclosporin	↔	↔		No dose adjustment of Epclusa or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be 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)		
	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 at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
	Sofosbuvir	↓ 0,97 (0,65 , 1,4)	↑ 1,1 (0,81 , 1,6)		
Tacrolimus	Effect on velpatasvir exposure not studied. *Expected:* ↔ Velpatasvir				

Medicine by therapeutic areas/Possible Mechanism of Interaction	**Effects on medicine 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]	Norel-gestromin	↔	↔	↔	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]	Norel-gestromin	↔	↔	↔	
	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 medicines 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 medicines 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

Use of Epclusa is contraindicated in pregnancy as the possibility of teratogenicity in humans of the velpatasvir component cannot be excluded.

Use of Epclusa combined with ribavirin is contraindicated in pregnancy as ribavirin is teratogenic (see PI of ribavirin).

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

Velpatasvir use in rabbits showed an increase in total visceral malformations in velpatasvir exposed animals at AUC exposures up to 0.7-fold the human exposed at clinical recommended doses. The human relevance of this finding is not known. Teratogenicity in humans cannot be excluded.

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 in women breastfeeding their babies. Women on treatment with Epclusa in combination with ribavirin, should not breastfeed their babies (See ribavirin PI).

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, consult the ribavirin PI for detailed recommendations regarding pregnancy, contraception, and breast-feeding.

4.7 Effects on ability to drive and use machines

Epclusa or Epclusa in combination with ribavirin, may influence the patient's ability to drive and use machines.

Patients should not drive and use machines until they know how they are affected by treatment with Epclusa or Epclusa combined with ribavirin.

4.8 Undesirable effects

a. 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.

b. Tabulated list of adverse events

In clinical trials, headache, fatigue and nausea were the most common (incidence ≥10 %) treatment emergent adverse events reported in patients treated with 12 weeks of Epclusa.

The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common

(≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

Frequency[a]	**Adverse drug reaction**
Gastrointestinal disorders	
Common	Nausea, diarrhoea, constipation, dyspepsia, abdominal pain, vomiting, abdominal distension
General Disorders and administration site conditions	
Very common	Fatigue
Common	Asthenia
Infections and infestations	
Common	Nasopharyngitis
Metabolism and nutrition disorders	
Common	Decreased appetite
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, muscle spasms
Nervous System Disorder	
Very common	Headache
Common	Dizziness, disturbance in attention
Psychiatric disorders	
Common	Insomnia, irritability, sleep disorder, depressed mood
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea
Skin and subcutaneous tissue disorders	
Common	Pruritus, rash

a Frequencies are based on the frequencies of treatment-emergent adverse events considered related to the drug by the investigator

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.

Patients with renal impairment

The safety profile of Epclusa has been evaluated in one open-label study (Study GS-US-342-4062) in which a total of 59 subjects with HCV and ESRD requiring dialysis received Epclusa for 12 weeks. The adverse events observed were consistent with expected clinical sequelae of ESRD.

Paediatric Population

The safety assessment of Epclusa in paediatric patients aged 12 years and older is based on data from a Phase 2, open-label clinical study (Study 1143) that enrolled 102 patients who were treated with sofosbuvir/velpatasvir for 12 weeks. The adverse reactions observed were consistent with those observed in clinical studies of Epclusa in adults.

Post-marketing experience

In addition to adverse reactions from clinical studies, the following adverse reactions were also identified during post approval use of Epclusa.

Adverse drug reaction
Skin and subcutaneous tissue disorders
Rash
Angioedema

Consult the ribavirin PI for side effects of ribavirin in patients on combination treatment with Epclusa and ribavirin

c. Description of selected adverse reactions

Cardiac dysrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens, such as Epclusa, are used in combination with amiodarone and/or other medicines that lower heart rate (see sections 4.4 and 4.5).

Skin disorders

Frequency Not known: Stevens-Johnson syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of Epclusa is important. It allows continued monitoring of the benefit/risk balance of Epclusa. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the 6.04 Adverse Drug Reactions Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity. 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 symptomatic and supportive treatment measures including monitoring of vital signs as well as observation of the clinical status of the patient. Hemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53 %. 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

A 20.2.8 Antiviral Agents.

Pharmacotherapeutic group: Antivirals for systemic use; Direct acting antiviral,

ATC code: J05AP55

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. GS-461203 is neither an inhibitor of

human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Velpatasvir is an 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 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 4. The EC_{50} 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 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.

Paediatric population

The presence of NS5A and NS5B RAVs did not impact treatment outcome in Study 1143; all patients with baseline NS5A (n=16) or NS5B NI (n=5) RAVs achieved sustained viral response (SVR) following 12 weeks treatment with Epclusa**.**

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

Clinical efficacy and safety

Paediatric population

The efficacy of 12 weeks of treatment with sofosbuvir/velpatasvir in HCV-infected paediatric patients aged 12 years and older with genotype 1,2,3,4 or 6 HCV infection was evaluated in a Phase 2, open-label clinical study in 102 patients with HCV infection.

A total of 80 patients (78%) were treatment-naïve and 22 patients (22%) were treatment-experienced. The median age was 15 years (range: 12 to 17); 51% of the patients were female; 73% were White, 9% were Black, and 11% were Asian; 14% were Hispanic/Latino; mean body mass index was 22.7 kg/m^2 (range: 12.9 to 48.9 kg/m^2); mean weight was 61 kg (range 22 to 147 kg); 58% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV infection were 74%, 6%, 12%, 2%, and 6%, respectively; no patients had known cirrhosis. The majority of patients (89%) had been infected through vertical transmission.

The SVR rate was 95% overall (97/102), 93% (71/76) in patients with genotype 1 HCV infection, and 100% in patients with genotype 2 (6/6), genotype 3 (12/12), genotype 4 (2/2), and genotype 6 (6/6) HCV infection. One patient who discontinued treatment early relapsed; the other four patients who did not achieve SVR12 did not meet virologic failure criteria (e.g., lost to follow-up).

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 patients and in patients with chronic hepatitis C (CHC). 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 AUC0-24 for sofosbuvir (N=982), GS-331007 (N=1428) and velpatasvir (N=1425) were 1260, 13970 and 2970 ng•hr/ml, respectively. Steady-state Cmax for sofosbuvir, GS-331007 and velpatasvir were 566, 868 and 259 ng/ml, respectively. Sofosbuvir and GS-331007 AUC0-24 and Cmax were similar in healthy adult patients and patients with HCV infection. Relative to healthy patients (N=331), velpatasvir AUC0-24 and Cmax 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 $AUC_{0\text{-}inf}$, respectively, and a

31 % and 5 % increase in velpatasvir Cmax, respectively. The moderate or high fat meal increased sofosbuvir AUC_{0-inf} by 60 % and 78 %, respectively, but did not substantially affect the sofosbuvir Cmax. The moderate or high fat meal did not alter GS-331007 AUC_{0-inf}, but resulted in a 25 % and 37 % decrease in Cmax, 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.

Distribution

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

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

Biotransformation

Sofosbuvir is extensively metabolized 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 catalyzed by human cathepsin A (Cat A) 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 [14C]-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 [14C]-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, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78 %) while 3.5 % was recovered as sofosbuvir. This 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 feces and urine, respectively. Unchanged velpatasvir was the major species in feces 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.

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, breast cancer resistance protein (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 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

Gender and Race

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

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 82 years) analyzed, age did not have a clinically relevant effect on the exposure to sofosbuvir, GS-331007, or velpatasvir.

Renal Impairment

The pharmacokinetics of sofosbuvir were studied in HCV negative adult 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 (see section 4.2).

The pharmacokinetics of sofosbuvir, GS-331007, and velpatasvir were studied in HCV-infected subjects with ESRD requiring dialysis treated with Epclusa for 12 weeks. Steady-state AUC_{tau} of sofosbuvir, GS-331007, and velpatasvir were increased by 81%, 1719%, and 41%, respectively.

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 patients with normal renal function, Velpatasvir AUC_{inf} was 50 % higher in patients with severe renal impairment (see section 4.2).

Hepatic Impairment

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected adult patients with moderate and severe hepatic impairment (CPT 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 adult patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative adult patients with moderate and severe hepatic impairment (CPT Class B and C). Compared to patients with normal hepatic function velpatasvir total plasma exposure (AUCinf) 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

In adults, body weight did not have a clinically significant effect on sofosbuvir or velpatasvir exposure according to a population pharmacokinetic analysis.

Paediatric Population

Sofosbuvir, GS-331007 and velpatasvir exposures in paediatric patients aged 12 years and older receiving oral once daily doses of sofosbuvir/velpatasvir 400 mg/100 mg were similar to those in adults receiving once daily doses of sofosbuvir/velpatasvir 400 mg/100 mg.

The pharmacokinetics of sofosbuvir, GS-331007 and velpatasvir in paediatric patients aged less than 12 years and weighing <30 kg have not been established.

5.3 Preclinical safety data

Sofosbuvir was found not to be genotoxic (in vitro & in vivo) or carcinogenic (mice and rats).

Velpatasvir was found not to be genotoxic (in vitro & in vivo) or carcinogenic (transgenic mouse and rats).

Sofosbuvir and Velpatasvir did not affect fertility in animal studies.

Reproductive toxicity: In rabbits an increase in total visceral malformations were observed in animals at velpatasvir AUC exposures up to 0.7-fold of human velpatasvir exposure with recommended clinical dosages

For ribavirin preclinical toxicity (See ribavirin PI).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

List of excipients: Tablet core:

Copovidone

Microcrystalline Cellulose

Croscarmellose Sodium

Magnesium Stearate

Film-Coat:

Polyvinyl alcohol, Titanium dioxide, Polyethylene glycol/Macrogol 3350, Talc, Iron oxide Red and Iron Oxide Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the container tightly closed.

6.5 Nature and contents of container

Epclusa 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 medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

51/20.2.8/0872

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 September 2020

10 DATE OF REVISION OF THE TEXT

10 March 2022

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