To be sold by retail on the prescription of " Gastroenterologist " only.

VELPACRUZ S
(Sofosbuvir + velpatasvir)

COMPOSITION

Each film-coated tablet contains:
Sofosbuvir 400 mg
Velpatasvir 100 mg
Excipients q.s.
Colours: Indigo Carmine Aluminium Lake, Brilliant Blue FCF Aluminium Lake and Titanium Dioxide I.P.

THERAPEUTIC INDICATIONS

Sofosbuvir+velpatasvir is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

POSOLOGY AND METHOD OF ADMINISTRATION

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

Posology

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

Table 1: Recommended treatment and duration for all HCV genotypes

Patient population[a]	Treatment and duration
Patients without cirrhosis and patients with compensated cirrhosis	Sofosbuvir+velpatasvir for 12 weeks Addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis.
Patients with decompensated cirrhosis	Sofosbuvir+velpatasvir + ribavirin for 12 weeks

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

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 Sofosbuvir+velpatasvir 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).

Patients should be instructed that if vomiting occurs within 3 hours of dosing an additional tablet of Sofosbuvir+velpatasvir should be taken. If vomiting occurs more than 3 hours after dosing, no further dose of Sofosbuvir+velpatasvir is needed.

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

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

Sofosbuvir+velpatasvir + ribavirin for 24 weeks may be considered.

Elderly

No dose adjustment is warranted for elderly patients.

Renal impairment

No dose adjustment of Sofosbuvir+velpatasvir is required for patients with mild or moderate renal impairment. The safety and efficacy of Sofosbuvir+velpatasvir 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.

Hepatic impairment

No dose adjustment of Sofosbuvir+velpatasvir is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C). Safety and efficacy of Sofosbuvir+velpatasvir have been assessed in patients with CPT Class B cirrhosis, but not in patients with CPT Class C cirrhosis.

Paediatric population

The safety and efficacy of Sofosbuvir+velpatasvir 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. Due to the bitter taste, it is recommended that the film-coated tablet is not chewed or crushed.

CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients.

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 Sofosbuvir + velpatasvir.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir. 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 Sofosbuvir+velpatasvir.

All patients receiving Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir + 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 Sofosbuvir+velpatasvir is required for patients with mild or moderate renal impairment. The safety of Sofosbuvir+velpatasvir has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) or ESRD requiring haemodialysis. When Sofosbuvir+velpatasvir is used in combination with ribavirin refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance < 50 mL/min.

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 Sofosbuvir+velpatasvir. Co-administration of such medicinal products with Sofosbuvir+velpatasvir is not recommended.

Use with certain HIV antiretroviral regimens

Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir 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.

HCV/HBV (hepatitis B virus) co-infection

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

CPT Class C cirrhosis

Safety and efficacy of Sofosbuvir+velpatasvir has not been assessed in patients with CPT Class C cirrhosis.

Liver transplant patients

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

DRUG INTERACTION

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

Potential for Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir

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 Sofosbuvir+velpatasvir is contraindicated. 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 Sofosbuvir+velpatasvir. Co-administration with such medicinal products is not recommended with Sofosbuvir+velpatasvir. 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 Sofosbuvir+velpatasvir mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir, a close monitoring of International Normalised Ratio (INR) values is recommended.

Interactions between Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir 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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
ACID REDUCING AGENTS					
					Velpatasvir solubility decreases as pH increases. Medicinal products 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 Sofosbuvir + velpatasvir administration by 4 hours.
H2-receptor antagonists					
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose) c Famotidine dosed simultaneously with Sofosbuvir+velpatasvird Cimetidine Nizatidine Ranitidine (Increase in gastric pH)	Sofosbuvir	↔	↔		H2-receptor antagonists may be administered simultaneously with or staggered from Sofosbuvir+velpatasvir 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)		

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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose)c Famotidine dosed 12 hours prior to Sofosbuvir+velpatasvird (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 Sofosbuvir+velpatasvird Lansoprazole Rabeprazole Pantoprazole Esomeprazole (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 Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvird	Sofosbuvir	↓ 0.79 (0.68, 0.92)	↔		
	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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
(Increase in gastric pH)		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 Sofosbuvir+velpatasvir.
Digoxin	Interaction only studied with velpatasvir. Expected: ↔ Sofosbuvir				Co-administration of Sofosbuvir+velpatasvir with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Sofosbuvir+velpatasvir.
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)		
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 Sofosbuvir+velpatasvir. A coagulation test helps to identify patients with an increased bleeding

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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
					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 Sofosbuvir+velpatasvir.
ANTICONVULSANTS					
Carbamazepine Phenytoin Phenobarbital (Induction of P-gp and CYPs)	Interaction not studied. Expected: ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir+velpatasvir is contraindicated with carbamazepine, phenobarbital and phenytoin, potent P-gp and CYP inducers.
Oxcarbazepine (Induction of P-gp and CYPs)	Interaction not studied. Expected: ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Sofosbuvir+velpatasvir with oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Sofosbuvir+velpatasvir. Co-administration is not recommended.
ANTIFUNGALS					
Ketoconazole	Interaction only studied with velpatasvir Expected: ↔ Sofosbuvir				No dose adjustment of Sofosbuvir+velpatasvir or ketoconazole is 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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
Ketoconazole (200 mg twice daily)/ velpatasvir (100 mg single dose)[d] (Inhibition of P-gp and CYPs)	Effect on ketoconazole exposure not studied. Expected: ↔ Ketoconazole				
Itraconazolee Voriconazolee Posaconazolee Isavuconazolee	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				Sofosbuvir+velpatasvir is contraindicated with rifampicin, a potent P-gp and CYP inducer.
	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)		
Rifabutin Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. Expected: ↓ Sofosbuvir				Sofosbuvir+velpatasvir is contraindicated with rifabutin, a potent P-gp and CYP inducer.

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 Sofosbuvir + Velpatasvir
	Active	Cmax	AUC	Cmin	
	↓ Velpatasvir				Co-administration of Sofosbuvir+velpatasvir with rifapentine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Sofosbuvir + velpatasvir. Co-administration is not recommended.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil fumarate	Sofosbuvir+velpatasvir has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and Cmax) was around 40-80% during co-treatment with Sofosbuvir+velpatasvir and tenofovir disoproxil fumarate/emtricitabine as part of various HIV regimens. Patients receiving tenofovir disoproxil fumarate and Sofosbuvir+velpatasvir 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.				
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600/ 200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)c, d	Efavirenz	↔	↔	↔	Co-administration of Sofosbuvir+velpatasvir with efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is expected to decrease the concentration of velpatasvir. Co-administration of Sofosbuvir+velpatasvir with efavirenz-containing regimens is not recommended.
	Sofosbuvir	↑ 1.2 (1.1, 1.7)	↔		
	Velpatasvir	↓ 0.53 (0.43, 0.64)	↓ 0.47 (0.39, 0.57)	↓ 0.43 (0.36, 0.52)	

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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
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 Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir, 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 Sofosbuvir+velpatasvir, 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	↓	↔	↔	

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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
		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 Sofosbuvir+velpatasvir, 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 Sofosbuvir+velpatasvir, 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 Sofosbuvir+velpatasvir or elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate is required.
	Cobicistat	↔	↔	↑ 2.0 (1.7, 2.5)	
	Tenofovir alafenamide	↔	↔		
	Sofosbuvir	↔	↑		

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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
			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 Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir or dolutegravir is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HERBAL SUPPLEMENTS					
St. John's wort (Induction of P-gp and CYPs)	Interaction not studied. Expected: ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir+velpatasvir is contraindicated with St. John's wort a potent P-gp and CYP inducer.
HMG-CoA REDUCTASE INHIBITORS					
Rosuvastatin	Interaction only studied with 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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
	Expected: ↔ Sofosbuvir				Co-administration of Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir.
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 Sofosbuvir+velpatasvir 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				
Other statins	Expected: ↑ Statins				Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with Sofosbuvir+velpatasvir, careful monitoring for statin adverse reactions should be undertaken

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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
					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 Sofosbuvir+velpatasvir or methadone is required.
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.3 (1.0, 1.7)		
Methadone	Interaction only studied with sofosbuvir Expected: ↔ Velpatasvir				
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)/ sofosbuvir (400 mg single dose)f	Ciclosporin	↔	↔		No dose adjustment of Sofosbuvir+velpatasvir 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)		
	Velpatasvir	↑ 1.6 (1.2, 2.0)	↑ 2.0 (1.5, 2.7)		
Tacrolimus	Tacrolimus	↓	↑		

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 Sofosbuvir + Velpatasvir**
	Active	**Cmax**	**AUC**	**Cmin**	
(5 mg single dose)f/ sofosbuvir (400 mg single dose)d		0.73 (0.59, 0.90)	1.1 (0.84, 1.4)		No dose adjustment of Sofosbuvir+velpatasvir or tacrolimus is required.
	Sofosbuvir	↓ 0.97 (0.65, 1.4)	↑ 1.1 (0.81, 1.6)		
Tacrolimus	Effect on velpatasvir exposure not studied. Expected: ↔ Velpatasvir				
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 Sofosbuvir+velpatasvir.

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%.

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 Sofosbuvir+velpatasvir in pregnant women.

Sofosbuvir

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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.

Velpatasvir

Animal studies have shown a possible link to reproductive toxicity.

As a precautionary measure, Sofosbuvir+velpatasvir 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, Sofosbuvir+velpatasvir should not be used during breast-feeding.

Fertility

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

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Sofosbuvir+velpatasvir has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

The safety assessment of Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir. These and other adverse events were reported at a similar frequency in placebo treated patients compared with Sofosbuvir+velpatasvir treated patients.

Patients with decompensated cirrhosis

The safety profile of Sofosbuvir+velpatasvir has been evaluated in one open-label study in which patients with CPT Class B cirrhosis received Sofosbuvir+velpatasvir for 12 weeks (n = 90), Sofosbuvir+velpatasvir + RBV for 12 weeks (n = 87) or Sofosbuvir+velpatasvir 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 Sofosbuvir+velpatasvir in combination with ribavirin.

Among the 87 patients who were treated with Sofosbuvir+velpatasvir + 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 Sofosbuvir+velpatasvir + 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.

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 Sofosbuvir+velpatasvir. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir+velpatasvir 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antiviral, ATC code: J05AX69

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 (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 the 50% inhibitory concentration (IC_{50}).

In vitro selection of HCV replicons with reduced susceptibility to velpatasvir was performed in cell culture for multiple genotypes including 1a, 1b, 2a, 3a, 4a, 5a and 6a. Variants were selected at NS5A resistance associated positions 24, 28, 30, 31, 32, 58, 92 and 93. The resistance associated variants (RAVs) selected in 2 or more genotypes were F28S, L31I/V and Y93H. Site-directed mutagenesis of known NS5A RAVs showed that substitutions conferring a > 100-fold reduction in velpatasvir susceptibility are M28G, A92K and Y93H/N/R/W in genotype 1a, A92K in genotype 1b, C92T and Y93H/N in genotype 2b, Y93H in genotype 3, and L31V and P32A/L/Q/R in genotype 6. No individual substitutions tested in genotypes 2a, 4a, or 5a conferred a > 100-fold reduction in velpatasvir susceptibility. Combinations of these

variants often showed greater reductions in susceptibility to velpatasvir than single RAVs alone.

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 sofosbuvir and velpatasvir has not been assessed in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

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 sofosbuvir and velpatasvir, 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 sofosbuvir and velpatasvir 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 sofosbuvir and velpatasvir with food or without food. Sofosbuvir and velpatasvir can be administered without regard to food.

Distribution

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

Velpatasvir is > 99.5% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 μg/mL to 1.8 μg/mL. After a single 100 mg dose of [^{14}C]-

velpatasvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.52 and 0.67.

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 biosysthesis 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 sofosbuvir and velpatasvir 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 sofosbuvir and velpatasvir was approximately 15 hours.

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, then 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.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE AND HANDLING INSTRUCTIONS
Store protected from moisture at a temperature not exceeding 30ºC.
Keep out of reach of children.
Keep the container tightly closed.

PRESENTATION
It is available in 28 tablets per bottle.

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