MyHep ALL
Sofosbuvir and Velpatasvir Film Coated Tablets
400 mg/100 mg

1. NAME OF THE MEDICINAL PRODUCT

Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet contains:
Sofosbuvir…….400 mg.
Velpatasvir……..100 mg.

Excipients with known effects: Each film-coated tablet contains 261.0 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet;

Light green to green colored, modified capsule shaped biconvex beveled edge film coated tablet debossed with **M** on one side and **SFV** on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

Table 1: Recommended treatment and duration for all HCV genotypes

Patient population[a]	**Treatment and duration**
Patients without cirrhosis and patients with compensated cirrhosis	Sofosbuvir and Velpatasvir tablet for 12 weeks Addition of ribavirin may be considered for genotype 3 infected patients with

	compensated cirrhosis (see section 5.1.)
Patients with decompensated cirrhosis	Sofosbuvir and Velpatasvir tablet + ribavirin for 12 weeks

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

When used in combination with ribavirin, refer also to the Summary of Product Characteristics of the medicinal product containing ribavirin.
The following dosing is recommended where ribavirin is divided in two daily doses and given with food:

Table 2: Guidance for ribavirin dosing when administered with Sofosbuvir and Velpatasvir tablet to patients with decompensated cirrhosis

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

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

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

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

If a dose of Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet at the usual time. Patients should be instructed not to take a double dose of Sofosbuvir and Velpatasvir tablet.

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

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

Renal impairment
No dose adjustment of Sofosbuvir and Velpatasvir tablet is required for patients with mild or moderate renal impairment. The safety and efficacy of Sofosbuvir and Velpatasvir tablet has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2) or end stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

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

Paediatric population
The safety and efficacy of Sofosbuvir and Velpatasvir tablet in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

For oral use.

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

4.3 Contraindications

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

Use with potent P-gp and potent CYP inducers

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

4.4 Special warnings and precautions for use

Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet 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 and Velpatasvir tablet. 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 and Velpatasvir tablet.

All patients receiving Sofosbuvir and Velpatasvir tablet 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 and 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 and Velpatasvir treatment in NS5A-naïve patients with baseline NS5A RAVs enrolled into the ASTRAL-studies, treatment with Sofosbuvir and Velpatasvir tablet + 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 and Velpatasvir tablet is required for patients with mild or moderate renal impairment. The safety of Sofosbuvir and Velpatasvir tablet has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) or ESRD requiring haemodialysis. When Sofosbuvir and Velpatasvir tablet is used in combination with ribavirin refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance < 50 mL/min (see section 5.2).

Use with moderate P-gp inducers or moderate CYP inducers

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

Use with certain HIV antiretroviral regimens

Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Refer to tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate Summary of Product Characteristics for recommendations on renal monitoring.

HCV/HBV (hepatitis B virus) co-infection

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

CPT Class C cirrhosis

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

Excipients

Sofosbuvir and Velpatasvir Film Coated Tablets contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Potential for Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet 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 and Velpatasvir tablet

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 and Velpatasvir. The use of such medicinal products with Sofosbuvir and Velpatasvir tablet is contraindicated (see section 4.3). Medicinal products that are moderate P-gp inducers or moderate CYP inducers (e.g. oxcarbazepine, modafinil or efavirenz) may decrease sofosbuvir or velpatasvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir and Velpatasvir tablet. Co-administration with such medicinal products is not recommended with Sofosbuvir and Velpatasvir tablet (see section 4.4). Co-administration with medicinal products that inhibit P-gp or BCRP may increase sofosbuvir or velpatasvir plasma concentrations. Medicinal products that inhibit OATP, CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir. Clinically significant medicinal product interactions with Sofosbuvir and Velpatasvir tablet mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir, a close monitoring of International Normalised Ratio (INR) values is recommended.

Interactions between Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir or velpatasvir and sofosbuvir as individual agents, or are predicted medicinal product interactions that may occur with Sofosbuvir and Velpatasvir. The table is not all-inclusive.

Table 3: Interactions between Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet**
	Active	**C_{max}**	**AUC**	**C_{min}**	
ACID REDUCING AGENTS					

					Velpatasvir solubility decreases as pH increases. Medicinal products that increase gastric pH are expected to decrease the concentration of velpatasvir.
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 and Velpatasvir tablet 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 and Velpatasvir tablet[d] Cimetidine[e] Nizatidine[e] Ranitidine[e] (Increase in gastric pH)	Sofosbuvir Velpatasvir	↔ ↓ 0.80 (0.70, 0.91)	↔ ↓ 0.81 (0.71, 0.91)		H2-receptor antagonists may be administered simultaneously with or staggered from Sofosbuvir and Velpatasvir tablet at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose)[c] Famotidine dosed 12 hours prior to Sofosbuvir and Velpatasvir tablet[d] (Increase in gastric pH)	Sofosbuvir Velpatasvir	↓ 0.77 (0.68, 0.87) ↔	↓ 0.80 (0.73, 0.88) ↔		
Proton pump inhibitors					

Omeprazole (20 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose fasted)[c] Omeprazole dosed simultaneously with Sofosbuvir and Velpatasvir tablet[d] Lansoprazole[e] Rabeprazole[e] Pantoprazole[e] Esomeprazole[e] (Increase in gastric pH)	Sofosbuvir Velpatasvir	↓ 0.66 (0.55, 0.78) ↓ 0.63 (0.50, 0.78)	↓ 0.71 (0.60, 0.83) ↓ 0.64 (0.52, 0.79)		Co-administration with proton pump inhibitors is not recommended. If it is considered necessary to co-administer, then Sofosbuvir and Velpatasvir tablet should be administered with food and taken 4 hours before proton pump inhibitor at max doses comparable to omeprazole 20 mg.
Omeprazole (20 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose fed)[c] Omeprazole dosed 4 hours after Sofosbuvir and Velpatasvir tablet[d] (Increase in gastric pH)	Sofosbuvir Velpatasvir	↓ 0.79 (0.68, 0.92) ↓ 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 and Velpatasvir tablet (see sections 4.4 and 4.8).
Digoxin	Interaction only studied with velpatasvir. *Expected:* ↔ Sofosbuvir				Co-administration of Sofosbuvir and Velpatasvir tablet with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is

					recommended when co-administered with Sofosbuvir and Velpatasvir tablet.
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 and Velpatasvir tablet. 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 sofosbuvir and velpatasvir.
ANTICONVULSANTS					
Carbamazepine Phenytoin Phenobarbital (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir and Velpatasvir tablet is contraindicated with carbamazepine, phenobarbital and phenytoin, potent P-gp and CYP inducers (see section 4.3).
Oxcarbazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:*				Co-administration of Sofosbuvir and Velpatasvir tablet with oxcarbazepine is

	↓ Sofosbuvir ↓ Velpatasvir				expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Sofosbuvir and Velpatasvir tablet. Co-administration is not recommended (see section 4.4).
ANTIFUNGALS					
Ketoconazole	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Sofosbuvir and Velpatasvir tablet or ketoconazole is required.
Ketoconazole (200 mg twice daily)/ velpatasvir (100 mg single dose)[d] (Inhibition of P-gp and CYPs) Itraconazole Voriconazole Posaconazole Isavuconazole	Effect on ketoconazole exposure not studied. *Expected:* ↔ Ketoconazole				
	Observed: Velpatasvir	↑ 1.3 (1.0, 1.6)	↑ 1.7 (1.4, 2.2)	↑ 1.3 (1.0, 1.6)	
ANTIMYCOBACTERIALS					
Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d] (Induction of P-gp and CYPs)	Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d] (Induction of P-gp and CYPs)				Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d] (Induction of P-gp and CYPs)
	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	Interaction not studied.				Sofosbuvir and Velpatasvir tablet is

Rifapentine (Induction of P-gp and CYPs)	*Expected:* ↓ Sofosbuvir ↓ Velpatasvir				contraindicated with rifabutin, a potent P-gp and CYP inducer (see section 4.3). Co-administration of Sofosbuvir and Velpatasvir tablet with rifapentine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Sofosbuvir and Velpatasvir tablet. Co-administration is not recommended (see section 4.4).
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil fumarate	Sofosbuvir and Velpatasvir tablet 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 Sofosbuvir and Velpatasvir tablet and tenofovir disoproxil fumarate/emtricitabine as part of various HIV regimens. Patients receiving tenofovir disoproxil fumarate and Sofosbuvir and Velpatasvir tablet concomitantly should be monitored for adverse reactions associated with tenofovir disoproxil fumarate. Refer to the tenofovir disoproxil fumarate-containing product's Summary of Product Characteristics for recommendations on renal monitoring (see section 4.4).				
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600/ 200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Efavirenz	↔	↔	↔	Co-administration of Sofosbuvir and Velpatasvir tablet with efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is expected to decrease the concentration of velpatasvir. Co-administration of Sofosbuvir and Velpatasvir tablet with efavirenz-containing regimens is not recommended (see section 4.4).
	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)	

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 and Velpatasvir tablet 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 and Velpatasvir tablet, 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 and Velpatasvir tablet, 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 Sofosbuvir and Velpatasvir tablet, 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 and Velpatasvir tablet, 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 and Velpatasvir tablet 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 Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet 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 and Velpatasvir tablet is contraindicated with St. John's wort a potent P-gp and CYP inducer (see section 4.3).
HMG-CoA REDUCTASE INHIBITORS					
Rosuvastatin	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				Co-administration of Sofosbuvir and Velpatasvir tablet with rosuvastatin increases the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin, at a dose
Rosuvastatin (10 mg single dose)/ velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B and BCRP)	*Observed:* Rosuvastatin	↑ 2.6 (2.3, 2.9)			
	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				

					that does not exceed 10 mg, may be administered with Sofosbuvir and Velpatasvir tablet.
Pravastatin	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet, 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 Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet 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 (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 Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet.
d. Lack of pharmacokinetics interaction bounds 70-143%.
e. These are medicinal products within class where similar interactions could be predicted.
f. Bioequivalence/Equivalence boundary 80-125%.
g. Lack of pharmacokinetics interaction bounds 50-200%.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Sofosbuvir
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
It has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose (see section 5.3).

Velpatasvir
Animal studies have shown a possible link to reproductive toxicity (see section 5.3).
As a precautionary measure, Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet should not be used during breast-feeding.

Fertility

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

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

4.7 Effects on ability to drive and use machines

Sofosbuvir and Velpatasvir tablet has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety assessment of Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet 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 and Velpatasvir tablet for 12 weeks. In clinical studies, headache, fatigue and nausea were the most common (incidence ≥ 10%) treatment emergent adverse events reported in patients treated with 12 weeks of Sofosbuvir and Velpatasvir tablet. These and other adverse events were reported at a similar frequency in placebo treated patients compared with Sofosbuvir and Velpatasvir tablet treated patients.

Patients with decompensated cirrhosis

The safety profile of Sofosbuvir and Velpatasvir tablet has been evaluated in one open-label study in which patients with CPT Class B cirrhosis received Sofosbuvir and Velpatasvir tablet for 12 weeks (n = 90), Sofosbuvir and Velpatasvir tablet + RBV for 12 weeks (n = 87) or Sofosbuvir and Velpatasvir tablet 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 and Velpatasvir tablet in combination with ribavirin.
Among the 87 patients who were treated with Sofosbuvir and Velpatasvir tablet + 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 and Velpatasvir tablet + RBV for 12 weeks due to adverse events.

Description of selected adverse reactions

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

Reporting of suspected adverse reactions

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

4.9 Overdose

The highest documented doses of sofosbuvir and velpatasvir were a single dose of 1,200 mg and a single dose of 500 mg, respectively. In these healthy volunteer studies, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

No specific antidote is available for overdose with Sofosbuvir and Velpatasvir tablet. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir and Velpatasvir tablet consists of general supportive measures including monitoring of vital signs, as well as observation of the clinical status of the patient. Haemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Haemodialysis is unlikely to result in significant removal of velpatasvir, since velpatasvir is highly bound to plasma protein.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antiviral, ATC code: not yet assigned
Namibia Pharmacological Classification: 20.2.8 – Antiviral agents

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	Median sofosbuvir	Number of	Median velpatasvir

	clinical isolates	EC_{50}, nM (range)	clinical isolates	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.

In clinical studies
Studies in patients without cirrhosis and patients with compensated cirrhosis

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

Of the 2 genotype 1 virologic failure patients, one patient had virus with emergent NS5A RAV Y93N and the other patient had virus with emergent NS5A RAVs L31I/V and Y93H at virologic failure. Both patients had virus at baseline harboring NS5A RAVs. No NS5B nucleoside inhibitor (NI) RAVs were observed at failure in the 2 patients.

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

Studies in patients with decompensated cirrhosis
In one Phase 3 study in patients with decompensated cirrhosis who received Sofosbuvir and Velpatasvir tablet + RBV for 12 weeks, 3 patients (1 with genotype 1 and 2 with genotype 3) qualified for resistance analysis due to virologic failure. No patients with genotype 2 or 4 HCV infection in the Sofosbuvir and Velpatasvir tablet + RBV 12 weeks group experienced virologic failure.

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

Of the 2 genotype 3 virologic failure patients, one had NS5A RAV Y93H emerge at failure. Another patient had virus with Y93H at baseline and virologic failure and also developed low levels (< 5%) of NS5B NI RAVs N142T and E237G at failure. Pharmacokinetic data from this patient was consistent with non-adherence to treatment.

In this study, 2 patients treated with Sofosbuvir and Velpatasvir tablet for 12 or 24 weeks without ribavirin had emergent NS5B S282T at low levels (< 5%) along with L159F.

Effect of baseline HCV resistance-associated variants on treatment outcome

Studies in patients without cirrhosis and patients with compensated cirrhosis
Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients without cirrhosis or with compensated cirrhosis in three Phase 3 clinical studies (ASTRAL-1, ASTRAL-2 and ASTRAL-3). Of the 1,035 patients treated with Sofosbuvir and Velpatasvir in the three Phase 3 clinical studies, 1,023 patients were included in the analysis of NS5A RAVs; 7 patients were excluded as they neither achieved sustained virologic response (SVR12) nor had virologic failure and 5 additional patients were excluded as NS5A gene sequencing failed. In the pooled analysis of the Phase 3 studies, 380/1,023 (37%) patients' virus had baseline NS5A RAVs. Genotype 2, 4, and 6 HCV-infected patients had a higher prevalence of NS5A RAVs (70%, 63% and 52%, respectively) compared to genotype 1 (23%), genotype 3 (16%), and genotype 5 (18%) HCV-infected patients.

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

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

Sofosbuvir and Velpatasvir tablet 12 weeks				
	Genotype 1	**Genotype 3**	**Genotypes 2, 4, 5 or 6**	**Total**
With any baseline NS5A RAVs	97% (73/75)	88% (38/43)	100% (262/262)	98% (373/380)
Without baseline NS5A RAVs	100% (251/251)	97% (225/231)	100% (161/161)	99% (637/643)

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

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

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

Studies in patients with decompensated cirrhosis (CPT Class B)

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

SVR12 in patients with or without baseline NS5A RAVs in the Sofosbuvir and Velpatasvir tablet + RBV 12 week group for this study is shown in Table 8.

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

Sofosbuvir and Velpatasvir tablet + RBV 12 weeks				
	Genotype 1	**Genotype 3**	**Genotypes 2 or 4**	**Total**
With any baseline NS5A RAVs	100% (19/19)	50% (1/2)	100% (4/4)	96% (24/25)
Without baseline NS5A RAVs	98% (46/47)	91% (10/11)	100% (2/2)	98% (58/60)

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

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

Cross-resistance

In vitro data suggests that the majority of NS5A RAVs that confer resistance to ledipasvir and daclatasvir remained susceptible to velpatasvir. Velpatasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all velpatasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and velpatasvir were fully active against substitutions associated with resistance to other classes of direct acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. The efficacy of Sofosbuvir and Velpatasvir tablet has not been assessed in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

Clinical efficacy and safety

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

Table 9: Studies conducted with Sofosbuvir and Velpatasvir tablet in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection

Study	**Population**	**Study arms (Number of patients treated)**
ASTRAL-1	Genotype 1, 2, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis	Sofosbuvir and Velpatasvir tablet 12 weeks (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2	Sofosbuvir and Velpatasvir

	TN and TE, without cirrhosis or with compensated cirrhosis	tablet 12 weeks (134) SOF+RBV 12 weeks (132)
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	Sofosbuvir and Velpatasvir tablet 12 weeks (277) SOF+RBV 24 weeks (275)
ASTRAL-4	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, with CPT Class B decompensated cirrhosis	Sofosbuvir and Velpatasvir tablet 12 weeks (90) Sofosbuvir and Velpatasvir tablet + RBV 12 weeks (87) Sofosbuvir and Velpatasvir tablet 24 weeks (90)

TN = treatment-naïve patients; TE = treatment-experienced patients (including those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor)

The ribavirin dose was weight-based (1,000 mg daily administered in two divided doses for patients < 75 kg and 1,200 mg for those ≥ 75 kg) and administered in two divided doses when used in combination with sofosbuvir in the ASTRAL-2 and ASTRAL-3 studies or in combination with Sofosbuvir and Velpatasvir tablet in the ASTRAL-4 study. Ribavirin dose adjustments were performed according to the ribavirin prescribing information. Serum HCV RNA values were measured during the clinical studies using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL. Sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment, was the primary endpoint to determine the HCV cure rate.

Clinical studies in patients without cirrhosis and patients with compensated cirrhosis

Genotype 1, 2, 4, 5 and 6 HCV-infected adults – ASTRAL-1 (study 1138)

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

Demographics and baseline characteristics were balanced between the Sofosbuvir and Velpatasvir tablet and placebo group. Of the 740 treated patients, the median age was 56 years (range: 18 to 82); 60% of the patients were male; 79% were White, 9% were Black; 21% had a baseline body mass index of at least 30 kg/m2; the proportions of patients with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5% and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels of at least 800,000 IU/mL; 19% had compensated cirrhosis; and 32% were treatment-experienced.

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

Table 10: SVR12 in study ASTRAL-1 by HCV genotype

	Sofosbuvir and Velpatasvir tablet 12 weeks (n = 624)							
	Total (all GTs) (n = 624)	**GT-1**			**GT-2 (n = 104)**	**GT-4 (n = 116)**	**GT-5 (n = 35)**	**GT-6 (n = 41)**
		GT-1a (n = 210)	**GT-1b (n = 118)**	**Total (n = 328)**				
SVR12	99% (618/624)	98% (206/210)	99% (117/118)	98% (323/328)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)
Outcome for patients without SVR12								
treatment virologic failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse[a]	< 1% (2/623)	< 1% (1/209)	1% (1/118)	1% (2/327)	0/104	0/116	0/35	0/41
Other[b]	1% (4/624)	1% (3/210)	0/118	1% (3/328)	0/104	0/116	3% (1/35)	0/41

GT = genotype

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

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

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

Demographics and baseline characteristics were balanced across the two treatment groups. Of the 266 treated patients, the median age was 58 years (range: 23 to 81); 59% of the patients were male; 88% were White, 7% were Black; 33% had a baseline body mass index of at least 30 kg/m2; 62% had non-CC IL28B alleles (CT or TT); 80% had baseline HCV RNA levels of at least 800,000 IU/mL; 14% had compensated cirrhosis and 15% were treatment-experienced.

Table 11 presents the SVR12 for the ASTRAL-2 study

Table 11: SVR12 in study ASTRAL-2 (HCV genotype 2)

	Sofosbuvir and Velpatasvir tablet. 12 weeks (n = 134)	**SOF+RBV 12 weeks (n = 132)**
SVR12	99% (133/134)	94% (124/132)
Outcome for patients without SVR12		
On-treatment virologic failure	0/134	0/132
Relapse[a]	0/133	5% (6/132)

Other[b]	1% (1/134)	2% (2/132)

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Treatment with Sofosbuvir and Velpatasvir tablet for 12 weeks demonstrated the statistical superiority (p = 0.018) over treatment with SOF+RBV for 12 weeks (treatment difference +5.2%; 95% confidence interval: +0.2% to +10.3%).

Genotype 3 HCV-infected adults – ASTRAL-3 (study 1140)
ASTRAL-3 was a randomised, open-label study that evaluated 12 weeks of treatment with Sofosbuvir and Velpatasvir tablet compared with 24 weeks of treatment with SOF+RBV in patients with genotype 3 HCV infection. Patients were randomised in a 1:1 ratio to treatment with Sofosbuvir and Velpatasvir tablet for 12 weeks or SOF+RBV for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis and prior treatment experience (treatment-naïve *versus* treatment-experienced).

Demographics and baseline characteristics were balanced across the two treatment groups. Of the 552 treated patients, the median age was 52 years (range: 19 to 76); 62% of the patients were male; 89% were White, 9% were Asian; 1% were Black; 20% had a baseline body mass index of at least 30 kg/m2; 61% had non-CC IL28B alleles (CT or TT); 70% had baseline HCV RNA levels of at least 800,000 IU/mL, 30% had compensated cirrhosis and 26% were treatment-experienced.

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

Table 12: SVR12 in study ASTRAL-3 (HCV genotype 3)

	Sofosbuvir and Velpatasvir tablet 12 weeks (n = 277)	**SOF+RBV 24 weeks (n = 275)**
SVR12	95% (264/277)	80% (221/275)
Outcome for patients without SVR12		
On-treatment virologic failure	0/277	< 1% (1/275)
Relapse[a]	4% (11/276)	14% (38/272)
Other[b]	1% (2/277)	5% (15/275)

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

Treatment with Sofosbuvir and Velpatasvir tablet for 12 weeks demonstrated the statistical superiority (p < 0.001) compared to treatment with SOF+RBV for 24 weeks (treatment difference +14.8%; 95% confidence interval: +9.6% to +20.0%).

SVR12 for selected subgroups are presented in Table 13.

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

	Sofosbuvir and Velpatasvir tablet 12 weeks		**SOF+RBV 24 weeks[a]**	
SVR12	Treatment-naïve (n = 206)	Treatment-experienced (n = 71)	Treatment-naïve (n = 201)	Treatment-experienced (n = 69)
Without cirrhosis	98% (160/163)	91% (31/34)	90% (141/156)	71% (22/31)
With cirrhosis	93% (40/43)	89% (33/37)	73% (33/45)	58% (22/38)

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

Clinical studies in patients with decompensated cirrhosis– ASTRAL-4 (study 1137)
ASTRAL-4 was a randomised, open-label study in patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection and CPT Class B cirrhosis. Patients were randomised in a 1:1:1 ratio to treatment with Sofosbuvir and Velpatasvir tablet for 12 weeks, Sofosbuvir and Velpatasvir tablet + RBV for 12 weeks or Sofosbuvir and Velpatasvir tablet for 24 weeks. Randomisation was stratified by HCV genotype (1, 2, 3, 4, 5, 6 and indeterminate).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 267 treated patients, the median age was 59 years (range: 40 to 73); 70% of the patients were male; 90% were White, 6% were Black; 42% had a baseline body mass index of at least 30 kg/m2. The proportions of patients with genotype 1, 2, 3, 4 or 6 HCV were 78%, 4%, 15%, 3%, and < 1% (1 patient), respectively. No patients with genotype 5 HCV infection were enrolled. 76% of the patients had non-CC IL28B alleles (CT or TT); 56% had baseline HCV RNA levels of at least 800,000 IU/mL, 55% were treatment-experienced; 90% and 95% of patients had CPT Class B cirrhosis and Model for End Stage Liver Disease (MELD) score ≤ 15 at baseline, respectively.

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

Table 14: SVR12 in study ASTRAL-4 by HCV genotype

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

a. n = 4 for genotype 2 and n = 4 for genotype 4
b. n = 4 for genotype 2 and n = 2 for genotype 4
c. n = 4 for genotype 2, n = 2 for genotype 4 and n = 1 for genotype 6.

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

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

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

	Sofosbuvir and Velpatasvir tablet 12 weeks	**Sofosbuvir and Velpatasvir tablet + RBV 12 weeks**	**Sofosbuvir and Velpatasvir tablet 24 weeks**
Virologic failure (relapse and on-treatment failure)			
Genotype 1[a]	7% (5/68)	1% (1/68)	4% (3/71)
Genotype 1a	6% (3/50)	2% (1/54)	4% (2/55)
Genotype 1b	11% (2/18)	0% (0/14)	6% (1/16)
Genotype 3	43% (6/14)	15% (2[b]/13)	42% (5[c]/12)
Other[d]	5% (4/82)	2% (2/81)	5% (4/83)

a. No patients with genotype 1 HCV had on-treatment virologic failure.
b. One patient had on-treatment virologic failure; pharmacokinetic data from this patient was consistent with non-adherence to treatment.
c. One patient had on-treatment virologic failure.
d. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria.

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

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

	Albumin	**Bilirubin**	**INR**	**Ascites**	**Encephalopathy**
Post-treatmentWeek 12 (N=236), %(n/N)					
Decreased score (Improvement)	34.5% (79/229)	17.9% (41/229)	2.2% (5/229)	7.9% (18/229)	5.2% (12/229)
No change	60.3% (138/229)	76.4% (175/229)	96.5% (221/229)	89.1% (204/229)	91.3% (209/229)
Increased score (Worsening)	5.2% (12/229)	5.7% (13/229)	1.3% (3/229)	3.1% (7/229)	3.5% (8/229)

No assessment	7	7	7	7	7
Post-treatment Week 24 (N=236),% (n/N)					
Decreased score (Improvement)	39.4% (84/213)	16.4% (35/213)	2.3% (5/213)	15.0% (32/213)	9.4% (20/213)
No change	54.0% (115/213)	80.8% (172/213)	94.8% (202/213)	81.2% (173/213)	88.3% (188/213)
Increased score (Worsening)	6.6% (14/213)	2.8% (6/213)	2.8% (6/213)	3.8% (8/213)	2.3% (5/213)
No assessment	23	23	23	23	23

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

Paediatric population

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

Elderly

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

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic properties of sofosbuvir, GS-331007 and velpatasvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Following oral administration of Sofosbuvir and Velpatasvir tablet, 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 tablet 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 C_{max}, respectively. The moderate or high fat meal increased sofosbuvir $AUC_{0\text{-}inf}$ by 60% and 78%, respectively, but did not substantially affect the sofosbuvir C_{max}. The moderate or high fat meal did not alter GS-331007 $AUC_{0\text{-}inf}$, but resulted in a 25% and 37% decrease in its C_{max}, respectively. The response rates in Phase 3 studies were similar in HCV-infected patients who received Sofosbuvir and Velpatasvir tablet with food or without food. Sofosbuvir and Velpatasvir tablet 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 tablet 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 tablet 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 and Velpatasvir drug-drug interations
Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Velpatasvir is also a substrate of OATP1B. *In vitro,* slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.

Velpatasvir is an inhibitor of drug transporter P-gp, BCRP, OATP1B1 and OATP1B3 and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant plasma concentration, velpatasvir is not an inhibitor of hepatic transporters bile salt export pump (BSEP), sodium taurocholate cotransporter protein (NTCP), OATP2B1, OATP1A2 or organic cation transporter (OCT) 1, renal transporters OCT2, OAT1, OAT3, multidrug resistance-associated protein 2 (MRP2) or multidrug and toxin extrusion protein (MATE) 1, or CYP or uridine glucuronosyltransferase (UGT) 1A1 enzymes.

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

Pharmacokinetics in special populations

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

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

Renal impairment
The pharmacokinetics of sofosbuvir was studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73 m2), moderate (eGFR ≥ 30 and < 50 mL/min/1.73 m2), severe renal impairment (eGFR < 30 mL/min/1.73 m2) and patients with ESRD requiring haemodialysis following a single 400

mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73 m2), the sofosbuvir $AUC_{0\text{-}inf}$ 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 velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). Relative to subjects with normal renal function, velpatasvir AUCinf was 50% higher in subjects with severe renal impairment (see section 4.2).

Hepatic impairment
The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (CPT Class B and C). Relative to patients with normal hepatic function, the sofosbuvir $AUC_{0\text{-}24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to sofosbuvir and GS-331007.

The pharmacokinetics of velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative patients with moderate and severe hepatic impairment (CPT Class B and C). Compared to subjects with normal hepatic function velpatasvir total plasma exposure (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
Body weight did not have a clinically significant effect on sofosbuvir or velpatasvir exposure according to a population pharmacokinetic analysis.

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

5.3 Preclinical safety data

Sofosbuvir

Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity and exposure to the major metabolite GS-331007 was instead used to estimate exposure margins.
Sofosbuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo*

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

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

Velpatasvir

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

Carcinogenicity studies with velpatasvir are ongoing.

Velpatasvir had no adverse effects on mating and fertility. No teratogenic effects were observed in the mouse and rat developmental toxicity studies with velpatasvir at AUC exposures approximately 31- and 6--fold higher, respectively, than the human exposure at the recommended clinical dose. However, a possible teratogenic effect was indicated in rabbits where an increase in total visceral malformations was seen in exposed animals at AUC exposures up to 0.7 fold the human exposure at recommended clinical dose. The human relevance of this finding is not known. Velpatasvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 5-fold higher than the human exposure at the recommended clinical dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core tablet

Copovidone, Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate

Film coat

Polyvinyl Alcohol, Polyethylene Glycol, Titanium Dioxide, Talc Indigo Carmine Aluminum Lake & Iron Oxide Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Bottle of 28's

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORIZATION HOLDER

Mylan Laboratories Limited, India.

Manufactured at

Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik - 422 113, Maharashtra, INDIA

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May 2017

REFERENCES

1. Epclusa: EMA - Product Information (Gilead Sciences Ireland UC)

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Botswana Regn No.:
Namibia Regn No.:
Namibia Scheduling Status: NS2

POM	Schedule 2	PP	List - 1

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