Summary of Product Characteristics

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 effect:

Each Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg contains about 261mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is a 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 Film Coated Tablets 400 mg/100 mg is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 6 years and older and weighing at least 17 kg (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg treatment should be initiated and monitored by a health care provider experienced in the management of patients with HCV infection.

Posology

The recommended dose of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg for adults and adolescents weighing more than 30 kg is one tablet, taken orally, once daily (see section 5.2).

The recommended dose of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg for children and adolescents aged 6 to < 18 years weighing between 17 and < 30 kg is half tablet, taken orally, once daily (see section 5.2).

†Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

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 Film Coated Tablets 400 mg/100 mg for 12 weeks
Patients with decompensated cirrhosis	Refer to specialist centre for treatment

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

Table 2: Recommended treatment and duration for adults and adolescents weighing ≥ 30 kg for all HCV genotypes

Body weight	Dose of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg	Sofosbuvir/Velpatasvir Daily Dose	Duration of treatment
≥ 30 kg	One tablet once daily	400 mg/100 mg per day	12 weeks

Patients should be instructed that if vomiting occurs within 3 hours of dosing an additional dose of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg should be taken. If vomiting occurs more than 3 hours after dosing, no further dose of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is needed (see section 5.1).

If a dose of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is missed and it is within 18 hours of the normal time, patients should be instructed to take the dose 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 Film Coated Tablets 400 mg/100 mg at the usual time. Patients should be instructed not to take a double dose of [HP026 trade name].

Elderly

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

Renal impairment

No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is required for patients with mild or moderate renal impairment.

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) and end stage renal disease (ESRD) requiring haemodialysis. Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg can be used in these patients with no dose adjustment when no other relevant treatment options are available (see section 4.4, 4.8, 5.1 and 5.2).

Hepatic impairment

No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg in children aged less than 6 years or weighing less than 17 kg has 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 ingredients or to any of the excipients listed in section 6.1.

Use with strong P-gp and strong CYP inducers
Medicinal products that are strong P-glycoprotein (P-gp) or strong cytochrome P450 (CYP) inducers (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort). Co-administration will significantly decrease sofosbuvir or velpatasvir plasma concentrations and could result in loss of efficacy of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg (see section 4.5).

4.4 Special warnings and precautions for us

Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg should not be administered concurrently with other medicinal products containing sofosbuvir.

Severe bradycardia and heart block
Life-threatening cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone. Bradycardia has generally occurred within hours to days, but cases with a longer time to onset have been observed mostly up to 2 weeks after initiating HCV treatment.
Amiodarone should only be used in patients on Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as outlined above 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 Film Coated Tablets 400 mg/100 mg.

All patients with concurrent or recent use of amiodarone should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

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.

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 and Velpatasvir Film Coated Tablets 400 mg/100 mg + 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
Safety data are limited in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and ESRD requiring haemodialysis. Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg can be used in these patients with no dose adjustment when no other relevant treatment options are available (see sections 4.8, 5.1 and 5.2).

Use with moderate P-gp inducers and/or moderate CYP inducers
Medicinal products that are moderate P-gp and/or moderate CYP inducers (e.g., efavirenz, modafinil, oxcarbazepine or rifapentine) may decrease sofosbuvir or velpatasvir plasma concentrations leading to reduced therapeutic effect of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg. Co-administration of such medicinal products with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is not recommended (see section 4.5).

Use with certain HIV antiretroviral regimens
Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil in the setting of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg with the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil or tenofovir disoproxil 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 Film Coated Tablets 400 mg/100 mg concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil or with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Refer to tenofovir disoproxil, emtricitabine/tenofovir disoproxil, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil Summary of Product Characteristics for recommendations on renal monitoring.

Use in diabetic patients

Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

CPT Class C cirrhosis

Safety and efficacy of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg in the treatment of HCV infection in patients who are post-liver transplant have not been assessed. Treatment with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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

The product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

As Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg contains sofosbuvir and velpatasvir, any interactions that have been identified with these active ingredients individually may occur with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg.

Potential for Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg.

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 strong inducers of P-gp or strong inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., carbamazepine, phenobarbital and phenytoin, rifampicin, rifabutin and St. John's wort) may decrease plasma concentrations of sofosbuvir or velpatasvir leading to reduced therapeutic effect of sofosbuvir/velpatasvir. The use of such medicinal products with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is contraindicated (see section 4.3). Medicinal

products that are moderate P-gp inducers or moderate CYP inducers (e.g., efavirenz, modafinil, oxcarbazepine or rifapentine) may decrease sofosbuvir or velpatasvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg. Co-administration with such medicinal products is not recommended with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg (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 Film Coated Tablets 400 mg/100 mg mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg, a close monitoring of International Normalised Ratio (INR) values is recommended.

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

Interactions between Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 and Velpatasvir Film Coated Tablets 400 mg/100 mg 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]**				**Recommendations concerning co-administration with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg**
	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 Film Coated Tablets 400 mg/100 mg administration by 4 hours.
H_2-receptor antagonists					
Famotidine (40 mg single dose) + sofosbuvir/ velpatasvir (400/ 100 mg single-dose)[c] Famotidine dosed simultaneously with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg[d] Cimetidine[e] Nizatidine[e] Ranitidine[e] (Increase in gastric pH)	Sofosbuvir	↔	↔		H_2-receptor antagonists may be administered simultaneously with or staggered from Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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)		
Famotidine (40 mg single dose) + sofosbuvir/ velpatasvir (400/100 mg single-dose)[c] Famotidine dosed 12 hours prior to Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg (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 and Velpatasvir Film Coated Tablets 400 mg/100 mg[d] Lansoprazole[e] Rabeprazole[e] Pantoprazole[e]	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 and Velpatasvir Film Coated Tablets 400 mg/100 mg should
	Velpatasvir	↓ 0.63 (0.50, 0.78)	↓ 0.64 (0.52, 0.79)		

Esomeprazole[e] (Increase in gastric pH)					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 Film Coated Tablets 400 mg/100 mg (Increase in gastric pH)	Sofosbuvir	↓ 0.79 (0.68, 0.92)	↔		
	Velpatasvir	↓ 0.67 (0.58, 0.78)	↓ 0.74 (0.63, 0.86)		
ANTIARRHYTHMICS					
Amiodarone	Effect on amiodarone, velpatasvir and sofosbuvir concentrations unknown				Co-administration of amiodarone with a sofosbuvir containing regimen may result in serious symptomatic bradycardia. Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg (see sections 4.4 and 4.8).
Digoxin	Interaction only studied with velpatasvir. *Expected:* ↔ Sofosbuvir				Co-administration of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg with digoxin may increase the concentration of
Digoxin (0.25 mg single dose)[f] + velpatasvir (100 mg single dose) (Inhibition of P-gp)	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				

					digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg
	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 Film Coated Tablets 400 mg/100 mg. 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 Film

					Coated Tablets 400 mg/100 mg.
ANTICONVULSANTS					
Phenytoin Phenobarbital (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is contraindicated with phenobarbital and phenytoin (see section 4.3).
Carbamazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir				Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is contraindicated with carbamazepine (see section 4.3).
	Observed: Sofosbuvir	↓ 0.52 (0.43, 0.62)	↓ 0.52 (0.46, 0.59)		
Oxcarbazepine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg with oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg. 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 Film Coated Tablets 400

					mg/100 mg or ketoconazole is required.
Ketoconazole (200 mg twice daily)/ velpatasvir (100 mg single dose)[d] (Inhibition of P-gp and CYPs) Itraconazole[e] Voriconazole[e] Posaconazole[e] Isavuconazole[e]	Effect on ketoconazole exposure not studied. *Expected:* ↔ Ketoconazole				
	Observed: Velpatasvir	↑ 1.3 (1.0, 1.6)	↑ 1.7 (1.4, 2.2)		
ANTIMYCOBACTERIALS					
Rifampicin (600 mg once daily)/sofosbuvir (400 mg single dose)[d] (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is contraindicated with rifampicin (see section 4.3).
	Observed: Sofosbuvir	↓ 0.23 (0.19, 0.29)	↓ 0.28 (0.24, 0.32)		
Rifampicin (600 mg once daily)/ velpatasvir (100 mg single dose) (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. *Expected:* ↔ Rifampicin				
	Observed: Velpatasvir	↓ 0.29 (0.23, 0.37)	↓ 0.18 (0.15, 0.22)		
Rifabutin (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Velpatasvir				Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg is contraindicated with rifabutin (see section 4.3).
	Observed: Sofosbuvir	↓ 0.64 (0.53, 0.77)	↓ 0.76 (0.63, 0.91)		
Rifapentine (Induction of P-gp and CYPs)	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ Velpatasvir				Co-administration of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg with rifapentine is

					expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of [HP026 trade name]. Coadministration is not recommended (see section 4.4).
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil	Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and C_{max}) was around 40-80% during cotreatment with [HP026 trade name]and tenofovir disoproxil /emtricitabine as part of various HIV regimens. Patients receiving tenofovir disoproxil and Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg concomitantly should be monitored for adverse reactions associated with tenofovir disoproxil. Refer to the tenofovir disoproxil-containing product's Summary of Product Characteristics for recommendations on renal monitoring (see section 4.4).				
Efavirenz/ emtricitabine/tenofovir disoproxil (600/200/300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Efavirenz	↔	↔	↔	Co-administration of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg with efavirenz/ emtricitabine/ tenofovir disoproxil is expected to decrease the concentration of velpatasvir. Co-administration of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg with efavirenz-containing regimens is not recommended (see section 4.4).
	Sofosbuvir	↑ 1.4 (1.1, 1.7)	↔		
	Velpatasvir	↓ 0.53 (0.43, 0.64)	↓ 0.47 (0.39, 0.57)	↓	
Emtricitabine/ **rilpivirine**/ tenofovir disoproxil	Rilpivirine	↔	↔	↔	No dose adjustment of

(200/25/300 mg once daily)/ sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Sofosbuvir	↔	↔		Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg or emtricitabine/ rilpivirine/ tenofovir disoproxil is required.
	Velpatasvir	↔	↔	↔	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS					
Atazanavir boosted with ritonavir (300/100 mg once daily) + emtricitabine/tenofovir disoproxil (200/300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Atazanavir	↔	↔	↑	No dose adjustment of [HP026 trade name], atazanavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil is required.
	Ritonavir	↔	↔	↑	
	Sofosbuvir	↔	↔		
	Velpatasvir	↑ 1.6 (1.4, 1.7)	↑ 2.4 (2.2, 2.6)	↑	
Darunavir boosted with ritonavir (800/100 mg once daily) + emtricitabine/tenofovir disoproxil (200/300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Darunavir	↔	↔	↔	No dose adjustment of [HP026 trade name], darunavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil 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 (200/300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Lopinavir	↔	↔	↔	No dose adjustment of [HP026 trade name], lopinavir (ritonavir boosted) or emtricitabine/tenofovir disoproxil is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.59 (0.49, 0.71)	↓ 0.7 (0.6, 0.8)		
	Velpatasvir	↓ 0.70 (0.59, 0.83)	↔	↑	
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400 mg twice daily)g + emtricitabine/tenofovir disoproxil (200/300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Raltegravir	↔	↔	↓	No dose adjustment of [HP026 trade name], raltegravir or emtricitabine/tenofovir disoproxil is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	Elvitegravir	↔	↔	↔	No dose adjustment of
	Cobicistat	↔	↔	↑	

(150/150/200/10 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Tenofovir alafenamide	↔			Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg or elvitegravir/ cobicistat/emtricitabine/ tenofovir alafenamide is required.
	Sofosbuvir	↔	↑ 1.4 (1.2, 1.5)		
	Velpatasvir	↑ 1.3 (1.2, 1.5)	↑ 1.5 (1.4, 1.7)	↑	
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (150/150/200/300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)c, d	Elvitegravir	↔	↔	↔	No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg or elvitegravir/ cobicistat/emtricitabine/ tenofovir disoproxil is required.
	Cobicistat	↔	↔	↑	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↑	
Dolutegravir (50 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)	Dolutegravir	↔	↔	↔	No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg is contraindicated with St. John's wort (see section 4.3).
HMG-CoA REDUCTASE INHIBITORS					
Atorvastatin (40 mg single dose) + sofosbuvir /velpatasvir (400/100 mg once daily)[d]	*Observed:* Atorvastatin	↑ 1.7 (1.5, 1.9)	↑ 1.5 (1.5, 1.6)		No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg or atorvastatin is required.
Rosuvastatin	Interaction only studied with velpatasvir *Expected:*				Co-administration

<table>
<tr><td rowspan="3">Rosuvastatin (10 mg single dose)/velpatasvir (100 mg once daily)d
(Inhibition of OATP1B and BCRP)</td><td colspan="4">↔ Sofosbuvir</td><td rowspan="3">of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 [HP026 trade name].</td></tr>
<tr><td>Observed:
Rosuvastatin</td><td>↑
2.6
(2.3, 2.9)</td><td>↑
2.7
(2.5, 2.9)</td><td></td></tr>
<tr><td colspan="4">Effect on velpatasvir exposure not studied
Expected:
↔ Velpatasvir</td></tr>
<tr><td>Pravastatin</td><td colspan="4">Interaction only studied with velpatasvir
Expected:
↔ Sofosbuvir</td><td></td></tr>
<tr><td rowspan="2">Pravastatin (40 mg single dose)/velpatasvir (100 mg once daily)d
(Inhibition of OATP1B)</td><td>Observed:
Pravastatin</td><td>↑
1.3
(1.1, 1.5)</td><td>↑
1.4
(1.2, 1.5)</td><td></td><td rowspan="2">No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg or pravastatin is required.</td></tr>
<tr><td colspan="4">Effect on velpatasvir exposure not studied
Expected:
↔ Velpatasvir</td></tr>
<tr><td>Other statins</td><td colspan="4">Expected:
↑ Statins</td><td>Interactions cannot be excluded with other HMG-CoA reductase inhibitors.
When co-administered with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg careful monitoring for statin adverse reactions should be undertaken and a reduced dose of statins should be considered if</td></tr>
</table>

					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 Film Coated Tablets 400 mg/100 mg or methadone is required.
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.3 (1.0, 1.7)		
Methadone	Interaction only studied with sofosbuvir *Expected:* ↔ Velpatasvir				No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg or methadone is required.
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)/ sofosbuvir (400 mg single dose)[f]	Ciclosporin	↔	↔		No dose adjustment of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
	Sofosbuvir	↑ 2.5 (1.9, 3.5)	↑ 4.5 (3.3, 6.3)		
Ciclosporin (600 mg single dose)[f]/ velpatasvir (100 mg single dose)[d]	Ciclosporin				
	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 Film Coated Tablets 400 mg/100 mg or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and
	Sofosbuvir	↓ 0.97 (0.65, 1.4)	↑ 1.1 (0.81, 1.6)		
Tacrolimus	Effect on velpatasvir exposure not studied. *Expected:* ↔ Velpatasvir				

					potential dose adjustment of tacrolimus may be required.
ORAL CONTRACEPTIVES					
Norgestimate/ethinyl estradiol (norgestimate 0.180 mg/0.215 mg/ 0.25 mg/ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily)[d]	Norel-gestromin	↔	↔	↔	No dose adjustment of oral contraceptives is required.
	Norgestrel	↔	↑ 1.2 (0.98, 1.5)	↑	
	Ethinyl estradiol	↔	↔	↔	
Norgestimate/ethinyl estradiol (norgestimate 0.180 mg/0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ velpatasvir (100 mg once daily)[d]	Norel-gestromin	↔	↔	↔	
	Norgestrel	↔	↔	↔	
	Ethinyl estradiol	↑ 1.4 (1.2, 1.7)	↔	↓	

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

[b] All interaction studies conducted in healthy volunteers.

[c] Administered as Epclusa.

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

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

[f] Bioequivalence/Equivalence boundary 80-125%.

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

4.6 Fertility, pregnancy, and breastfeeding

Pregnancy:

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir, velpatasvir or Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg should not be used during breast-feeding.

Fertility:
No human data on the effect of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg on fertility are available. Animal studies do not indicate harmful effects of sofosbuvir or velpatasvir on fertility.
If ribavirin is co-administered with [HP026 trade name], refer to the Summary of Product Characteristics for ribavirin for detailed recommendations regarding pregnancy, contraception, and breast-feeding.

4.7 Effects on ability to drive and use machines
Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
In pooled Phase 3 clinical studies of patients with genotype 1, 2, 3, 4, 5 or 6 HCV infection 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 ≥ 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 in the Phase 3 pivotal clinical studies.

Assessment of adverse reactions for sofosbuvir/velpatasvir is based on post-marketing surveillance for sofosbuvir/velpatasvir-containing products.
Common (> 1%):
• Rash (not specified)
Uncommon (> 0.1%):
• Angioedema

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.

Patients with renal impairment:
The safety of sofosbuvir/velpatasvir has been evaluated in a 12-week non-controlled study including 59 subjects with ESRD requiring dialysis (Study 4062). In this setting, exposure of sofosbuvir metabolite GS-331007 was 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients.

Description of suspected adverse reactions:

Cardiac arrhythmias
Cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone and/or other medicinal products that lower heart rate (see sections 4.4 and 4.5).

Skin disorders
Frequency not known: Stevens-Johnson syndrome.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

For reporting of adverse events and PV related queries please write to Email: ProductSafety@viatris.com

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, no untoward effects were 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 Film Coated Tablets 400 mg/100 mg. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg 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: Antivirals for systemic use; Direct acting antiviral, ATC code: J05AP55

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine 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 6. The EC_{50} values of sofosbuvir and velpatasvir against clinical isolates are presented in Table 7.

Table 4: Activity of sofosbuvir and velpatasvir against full-length or chimeric laboratory replicons

Replicon genotype	Sofosbuvir EC50, nM[a]	Velpatasvir EC50, nM[a]
1a	40	0.014
1b	110	0.016
2a	50	0.005-0.016c
2b	15b	0.002-0.006c
3a	50	0.004
4a	40	0.009
4d	NA	0.004
5a	15b	0.021-0.054d
6a	14b	0.006-0.009
6e	NA	0.130d

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.

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 400 mg/100 mg Film Coated Tablets 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 harbouring 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 400 mg/100 mg Film Coated Tablets + 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 Film Coated Tablets 400 mg/100 mg + 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 Film Coated Tablets 400 mg/100 mg for 12 or 24 weeks without ribavirin had emergent NS5B S282T at low levels (< 5%) along with L159F.

Effect of baseline HCV resistance-associated variants on treatment outcome

Studies in patients without cirrhosis and patients with compensated cirrhosis

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome for patients without cirrhosis or with compensated cirrhosis in three Phase 3 clinical

studies (ASTRAL-1, ASTRAL-2 and ASTRAL-3). Of the 1,035 patients treated with sofosbuvir/velpatasvir in the three Phase 3 clinical studies, 1,023 patients were included in the analysis of NS5A RAVs; 7 patients were excluded as they neither achieved sustained virologic response (SVR12) nor had virologic failure and 5 additional patients were excluded as NS5A gene sequencing failed. In the pooled analysis of the Phase 3 studies, 380/1,023 (37%) patients' virus had baseline NS5A RAVs. Genotype 2, 4, and 6 HCV-infected patients had a higher prevalence of NS5A RAVs (70%, 63% and 52%, respectively) compared to genotype 1 (23%), genotype 3 (16%), and genotype 5 (18%) HCV-infected patients.

Baseline RAVs had no relevant impact on SVR12 rates in patients infected with genotype 1, 2, 4, 5 and 6 HCV, as summarised in Table 8. 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 400 mg/100 mg Film Coated Tablets for 12 weeks, as summarised in Table 9. In the ASTRAL-3 study, the Y93H RAV was detected at baseline in 9% of patients treated with Sofosbuvir and Velpatasvir.

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 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 12 Weeks		
	All Subjects (n = 274)	**Cirrhotic (n = 80)**	**Non-Cirrhotic (n = 197)**
Overall 95% CI	95.3% (263/274) 92.9% to 98.0%	91.3 (73/80) 82.8% to 96.4%	97.9% (190/194) 92.8% to 98.6%
SVR with Y93H 95% CI	84.0% (21/25) 63.9% to 95.5%	50.0% (2/4) 6.8% to 93.2%	90.5% (19/21) 69.6 to 98.8%
SVR without Y93H 95% CI	96.4% (242/249) 94.3% to 98.9%	93.4% (71/76) 85.3% to 97.8%	98.8% (171/173) 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 + 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 + 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 400 mg/100 mg Film Coated Tablets + RBV 12 week group for this study is shown in Table 10.

Table 10: SVR12 in patients with or without baseline NS5A RAVs by HCV genotype (study ASTRAL-4)

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

Paediatric population

The presence of NS5A and NS5B RAVs did not impact treatment outcome; all patients with baseline NS5A (n=29) or NS5B NI (n=6) RAVs achieved SVR following 12 weeks treatment with Sofosbuvir and Velpatasvir 400 mg/100 mg Film Coated Tablets.

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 Film Coated Tablets 400 mg/100 mg 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 was evaluated in three Phase 3 studies in patients with genotype 1 to 6 HCV infection with or without compensated cirrhosis, one Phase 3 study in patients with

genotype 1 to 6 HCV infection with decompensated cirrhosis, one Phase 3 study in HCV/HIV-1 co-infected patients with genotype 1 to 6 HCV infection and one Phase 2 study in patients with HCV infection and ESRD requiring dialysis, as summarised in Table 11.

Table 9: Studies conducted with Sofosbuvir and Velpatasvir 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 (624) Placebo 12 weeks (116)
ASTRAL-2	Genotype 2 TN and TE, without cirrhosis or with compensated cirrhosis	Sofosbuvir and Velpatasvir 12 weeks (134) SOF+RBV 12 weeks (132)
ASTRAL-3	Genotype 3 TN and TE, without cirrhosis or with compensated cirrhosis	Sofosbuvir and Velpatasvir 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 12 weeks (90) Sofosbuvir and Velpatasvir + RBV 12 weeks (87) Sofosbuvir and Velpatasvir 24 weeks (90)
ASTRAL-5	Genotype 1, 2, 3, 4, 5 and 6 TN and TE, without cirrhosis or with compensated cirrhosis, with HCV/HIV-1 co-infection	Sofosbuvir and Velpatasvir 12 weeks (106)
GS-US-342-4062	TN and TE with or without cirrhosis, with ESRD requiring dialysis	Sofosbuvir and Velpatasvir 12 weeks (59)

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 400 mg/100 mg Film Coated Tablets 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 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 for 12 weeks or placebo for 12 weeks. Patients with genotype 5 HCV infection were enrolled to the Sofosbuvir and Velpatasvir 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 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/m^2; the proportions of patients with genotype 1, 2, 4, 5, or 6 HCV infection were 53%, 17%, 19%, 5% and 7%, respectively; 69% had non-CC IL28B alleles (CT or TT); 74% had baseline HCV RNA levels 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 12 weeks (n = 624)							
	Total (all GTs) (n = 624)	**GT-1**			**GT-2 (n = 104)**	**GT-4 (n = 116)**	**GT-5 (n = 35)**	**GT-6 (n = 41)**
		GT-1a (n = 210)	**GT-1b (n = 118)**	**Total (n = 328)**				
SVR12	99% (618/624)	98% (206/210)	99% (117/118)	98% (323/328)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)
Outcome for patients without SVR12								
On-treatment virologic failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapsea	< 1% (2/623)	< 1% (1/209)	1% (1/118)	1% (2/327)	0/104	0/116	0/35	0/41
Otherb	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 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 for 12 weeks or SOF+RBV for 12 weeks. Randomization 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/m^2; 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 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 Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg 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 Film Coated Tablets 400 mg/100 mg 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/m^2; 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 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 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 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 for 12 weeks, Sofosbuvir and Velpatasvir + RBV for 12 weeks or Sofosbuvir and Velpatasvir 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/m^2. The proportions

of patients with genotype 1, 2, 3, 4 or 6 HCV were 78%, 4%, 15%, 3%, and < 1% (1 patient), respectively. No patients with genotype 5 HCV infection were enrolled. 76% 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 12 weeks (n = 90)	**Sofosbuvir and Velpatasvir + RBV 12 weeks (n = 87)**	**Sofosbuvir and Velpatasvir 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 12 weeks	**Sofosbuvir and Velpatasvir + RBV 12 weeks**	**Sofosbuvir and Velpatasvir 24 weeks**
Virologic failure (relapse and on-treatment failure)			
Genotype 1a	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% (2b/13)	42% (5c/12)
Otherd	5% (4/82)	2% (2/81)	5% (4/83)

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

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

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

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

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

Clinical studies in patients with HCV/HIV-1 Co-infection – ASTRAL-5 (study 1202)
ASTRAL-5 evaluated 12 weeks of treatment with Sofosbuvir and Velpatasvir 400 mg/100 mg Film Coated Tablets in patients with genotype 1, 2, 3, or 4 HCV infection who were co-infected with HIV-1 (HCV genotype 5 and 6 allowed, but no such patients were included). Patients were on a stable HIV-1 antiretroviral therapy that included emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine administered with a ritonavir boosted protease inhibitor (atazanavir, darunavir, or lopinavir), rilpivirine, raltegravir or emtricitabine/tenofovir disoproxil fumarate /elvitegravir/cobicistat.

Of the 106 treated patients, the median age was 57 years (range: 25 to 72); 86% of the patients were male; 51% were White; 45% were Black; 22% had a baseline body mass index ≥ 30 kg/m^2; 19 patients (18%) had compensated cirrhosis; and 29% were treatment experienced. The overall mean CD4+ count was 598 cells/µL (range: 183−1513 cells/µL).

Table 17 presents the SVR12 for the ASTRAL-5 study by HCV genotype.

Table 17: SVR12 in study ASTRAL-5 by HCV genotype

	Sofosbuvir and Velpatasvir 12 weeks (n = 106)						
	Total (all GTs) (n = 106)	**GT-1**			**GT-2 (n = 11)**	**GT-3 (n = 12)**	**GT-4 (n = 5)**
		GT-1a (n = 66)	**GT-1b (n = 12)**	**Total (n = 78)**			
SVR12	95% (101/106)	95% (63/66)	92% (11/12)	95% (74/78)	100% (11/11)	92% (11/12)	100% (5/5)
Outcome for patients without SVR							
On-treatment virologic failure	0/106	0/66	0/12	0/78	0/11	0/12	0/5
Relapse[a]	2% (2/103)	3% (2/65)	0/11	3% (2/76)	0/11	0/11	0/5
Other[b]	3% (3/106)	2% (1/66)	8% (1/12)	3% (2/78)	0/11	8% (1/12)	0/5

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.

SVR12 was achieved by 19/19 patients with cirrhosis. No patient had HIV-1 rebound during the study, and CD4+ counts were stable during treatment.

Clinical studies in patients with Renal Impairment – study 4062

Study 4062 was an open-label clinical study that evaluated 12 weeks of treatment with Sofosbuvir and Velpatasvir in 59 HCV-infected patients with ESRD requiring dialysis. The proportions of patients with genotype 1, 2, 3, 4, 6 or indeterminate HCV infection were 42%, 12%, 27%, 7%, 3%, and 9%, respectively. At baseline, 29% of patients had cirrhosis, 22% were treatment experienced, 32% had received a kidney transplant, 92% were on haemodialysis, and 8% were on peritoneal dialysis; mean duration on dialysis was 7.3 years (range: 0 to 40 years). The overall SVR rate was 95% (56/59); of the three patients that did not achieve SVR12, one had completed Sofosbuvir and Velpatasvir 400 mg/100 mg Film Coated Tablets treatment and relapsed and two did not meet virologic failure criteria.

Paediatric population

The efficacy of 12 weeks of treatment with sofosbuvir/velpatasvir in HCV-infected paediatric patients aged 3 years and older was evaluated in a Phase 2, open-label clinical study in 214 patients with HCV infection.

Patients aged 12 to < 18 Years:
Sofosbuvir/velpatasvir was evaluated in 102 patients aged 12 to <18 years with genotype 1, 2, 3, 4, or 6 HCV infection. A total of 80 patients (78%) were treatment-naïve and 22 patients (22%) were treatment-experienced. The median age was 15 years (range: 12 to 17); 51% of the patients were female; 73% were White, 9% were Black, and 11% were Asian; 14% were Hispanic/Latino; mean body mass index was 22.7 kg/m^2 (range: 12.9 to 48.9 kg/m^2); mean weight was 61 kg (range 22 to 147 kg); 58% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV infection were 74%, 6%, 12%, 2%, and 6%, respectively; no patients had known cirrhosis. The majority of patients (89%) had been infected through vertical transmission.

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

Patients aged 6 to < 12 Years:
Sofosbuvir/velpatasvir was evaluated in 71 patients aged 6 to <12 years with genotype 1, 2, 3, and 4 HCV infection. A total of 67 patients (94%) were treatment-naïve and 4 patients (6%) were treatment-experienced. The median age was 8 years (range: 6 to 11); 54% of the patients were female; 90% were White, 6% were Black, and 1% were Asian; 10% were Hispanic/Latino; mean body mass index was 17.4 kg/m^2 (range: 12.8 to 30.9 kg/m^2); mean weight was 30 kg (range 18 to 78 kg); 48% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; the proportions of patients with genotype 1, 2, 3, or 4 HCV infection were 76%, 3%, 15%, and 6%, respectively; no patients had known cirrhosis. The majority of patients (94%) had been infected through vertical transmission.

The SVR rate was 93% overall (66/71), 93% (50/54) in patients with genotype 1 HCV infection, 91% (10/11) in patients with genotype 3 HCV infection, and 100% in patients with genotype 2 (2/2) and genotype 4 (4/4) HCV infection. One subject had on-treatment virologic failure; the other four patients who did not achieve SVR12 did not meet virologic failure criteria (e.g., lost to follow-up).

Elderly
Clinical studies of sofosbuvir/velpatasvir 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 of Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg

The absorption characteristics of sofosbuvir in Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg have been determined after administration of a single dose tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value ± standard deviation (*)
	Sofosbuvir
Maximum concentration (C_{max})	1754 ± 653 (1635) ng/ml
Area under the curve (AUC_{0-72}), a measure of the extent of absorption	1993 ± 651 (1890) ng.h/ml

Time to attain maximum concentration (t_{max})	1.03 ± 0.69 h

* geometic mean

The absorption characteristics of velpatasvir in Sofosbuvir and Velpatasvir Film Coated Tablets 400 mg/100 mg have been determined after administration of a single dose tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value ± standard deviation (*)
	Velpatasvir
Maximum concentration (C_{max})	417 ± 189 (367) ng/ml
Area under the curve (AUC_{0-72}), a measure of the extent of absorption	3960 ± 1922 (3417) ng.h/ml
Time to attain maximum concentration (t_{max})	3.02 ± 0.87 h

* geometic mean

Pharmacokinetic of Sofosbuvir and Velpatasvir

	Sofosbuvir	**Velpatasvir**
General		
	Sofosbuvir is a nucleotide prodrug that is extensively metabolised.	
Absorption		
Oral Bioavailability	At least 82.5%	NA
	T_{max} 1 hr	T_{max} 3 hr
Food effect		
Moderate fat (30%) meal	AUC_{0-inf} ↑ 60%	AUC_{0-inf} ↑ 34%
High fat (50%) meal	AUC_{0-inf} ↑ 78%	AUC_{0-inf} ↑ 21%
Distribution		
Volume of distribution (mean)	Vc 197 L	Vc 392 L
Plasma protein binding in vitro	85% independent of concentration GS-331007 is minimally protein-bound	> 99.5% independent of concentration
Tissue distribution	Blood/plasma ratio: 0.7	Blood/plasma ratio: 0.52-0.67
Metabolism		
	The active triphosphate metabolite GS-461203 is formed in the liver by extensive metabolism via sequential hydrolysis (Cat A or CES1) and phosphoramidate cleavage (HINT1) followed by	

	phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of the inactive nucleoside metabolite GS-331007. Sofosbuvir and GS-331007 are not substrates of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes. CYP2B6, CYP2C8, and CYP3A4, with slow turnover.	
Active metabolite(s)	The active metabolite GS-461203 is formed in hepatocytes and not observed in plasma.	None
Elimination		
Elimination half-life	Sofosbuvir 0.4 hr	19 hr
Mean systemic clearance (Cl/F)	352 L/h	47 L/h
% of dose excreted in urine	80% (mainly as GS-331007; 3.5% as sofosbuvir)	0.4%
% of dose excreted in faeces	14%	94% (77% as parent compound)
Pharmacokinetic linearity	Near dose-proportional over the dose range 200 mg to 1200 mg	Near dose-proportional over the dose range 25 mg to 150 mg
Drug interactions Sofosbuvir is a substrate of P-gp and BCRP.	Sofosbuvir is a substrate for CatA and CES1, followed by HINT1, however no interaction in vivo is expected involving this pathway.	Substrate of CYP2B6, CYP2C8, CYP3A4 and OATP1B. Inhibitor of P-gp, BCRP, OATP1B1 and OATP1B3

NA: not available

Pharmacokinetics in special populations

Gender and race

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

Elderly

Population pharmacokinetic analysis in HCV infected subjects 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 and velpatasvir.

Renal impairment

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73 m^2), moderate (eGFR ≥30 and <50 mL/min/1.73 m^2), severe renal impairment (eGFR <30 mL/min/1.73 m^2) and subjects with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR >80 mL/min/1.73 m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir $AUC_{0\text{-}inf}$ was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when sofosbuvir was dosed 1 hour after haemodialysis. The $AUC_{0\text{-}inf}$ of GS-331007 in subjects with ESRD could not be reliably determined. However, data indicate at least 10-fold and 20-fold higher exposure to GS-331007 in ESRD compared to normal subjects when sofosbuvir was administered 1 hour before or 1 hour after haemodialysis, respectively.
Haemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. A 4-hour haemodialysis session removed approximately 18% of administered dose.
For velpatasvir, in HCV negative subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and subjects with ESRD requiring haemodialysis $AUC_{0\text{-}inf}$ was 1.5- and 1.4-fold higher, respectively.

Hepatic impairment
The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV infected subjects with moderate and severe hepatic impairment (CPT class B and C). Relative to subjects 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 subjects indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007.
The pharmacokinetics of velpatasvir was studied with a single dose of 100 mg velpatasvir in HCV negative patients with moderate and severe hepatic impairment (CPT Class B and C). Compared to subjects with normal hepatic function velpatasvir total plasma exposure ($AUC_{0\text{-}inf}$) was similar in patients with moderate or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to velpatasvir.

Paediatric population
Sofosbuvir and GS-331007 exposures in adolescents aged 12 to < 18 years were similar to those in adults from Phase 2/3 studies following administration of sofosbuvir (400 mg). The pharmacokinetics of sofosbuvir and GS-331007 have not been established in paediatric patients below 12 years of age.

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. Velpatasvir was not carcinogenic in the 6-month rasH2 transgenic mouse and 2-year rat carcinogenicity studies at exposures at least 50-times and 5-times higher than human exposure, respectively.

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 , Titanium dioxide , Macrogol/polyethylene glycol , Talc , FD&C blue #2/ Indigo carmine aluminium 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

7. SUPPLIER

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad – 500096
Telangana
India
Email: ProductSafety@viatris.com

8. MFG. BY:

Mylan Laboratories Limited,
F-4 & F-12, MIDC, Malegaon,
Sinnar, Nashik – 422113,
Maharashtra, India.

9. DATE OF REVISION OF THE TEXT

January 2021
Section 6 was updated in May 2021
Section 3 was updated in July 2022

References

Epclusa 400 mg/100 mg film-coated tablets
PIL (UK)
Last revised 08/2020

Epclusa 400 mg/100 mg film coated tablets
Summary of Product Characteristics (EMA)
Last revised 08/2020

Epclusa Assessment report
Committee for Medicinal Products for Human Use (CHMP) May 26, 2016
https://www.ema.europa.eu/en/documents/assessment-report/epclusa-epar-public-assessment-report_en.pdf

Teresa Brieva, Antonio Rivero & Antonio Rivero-Juarez, Pharmacokinetic drug evaluation of velpatasvir plus sofosbuvir for the treatment of hepatitis C virus infection, Expert Opinion on Drug & Toxicology, 13:4, 483-490, DOI:10.1080/17425255.2017.1292253

Brian J. Kirby, William T. Symonds, Brian P. Kearney, Anita A. Mathias, Pharmacokinetic, Pharmacodynamic, and Drug-Interaction Profile of the Hepatitis C Virus NS5B Polymerase Inhibitor Sofosbuvir, Clin Pharmacokinet (2015) 54:677–690, DOI 10.1007/s40262-015-0261-7

World Health Organization Guidelines for the Care and Treatment of Persons diagnosed with Chronic Hepatitis C Virus Infection July 2018
https://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2018/en/

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines

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Rwanda Regn No.: Rwanda FDA-HMP-MA-0139
Zambia Regn No.:
Zimbabwe Regn No.: 2021/7.13/6200
Botswana Regn No.: BOT2103692
Namibia Regn No.:
Namibia Scheduling Status.: NS2

POM | **Schedule 2** | **PP** | **List - 1**

