OCVIR®-V Tablets

(Sofosbuvir + Velpatasvir)

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with **OCVIR®-V**. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

QUALITATIVE & QUANTITATIVE COMPOSITION

OCVIR®-V 400mg/100mg Tablets
Each film coated tablet contains:
Sofosbuvir MS……400mg
Velpatasvir MS.....100mg

PHARMACEUTICAL FORM

Tablets

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS: OCVIR®-V is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult and paediatric patients 6 years of age and older or weighing at least 17 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection.

- without cirrhosis or with compensated cirrhosis.
- with decompensated cirrhosis for use in combination with ribavirin.

POSOLOGY AND METHOD OF ADMINISTRATION: Posology: OCVIR®-V treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection. The recommended dose of **OCVIR®-V** is one tablet, taken orally, once daily with or without food. ***Testing Prior to the Initiation of Therapy:*** Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment. ***Recommended Treatment Regimen and Duration in Patients 6 Years of Age and Older or Weighing at Least 17kg:*** Table 1 shows the recommended treatment regimen and duration based on patient population. For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 1. For treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis or with compensated cirrhosis (Child-Pugh A), the recommended regimen is once daily for 12 weeks

Table 1: Recommended Treatment Regimen and Duration in Patients 6 Years of Age and Older or Weighing at Least 17kg with Genotype 1, 2, 3, 4, 5, or 6 HCV

Patient Population	Treatment Regimen and Duration
Treatment-naïve and treatment-experienced, without cirrhosis and with compensated cirrhosis (Child-Pugh A)	**OCVIR®-V** 12 weeks
Treatment-naïve and treatment-experienced, with decompensated cirrhosis (Child-Pugh B or C)	**OCVIR®-V** + ribavirin 12 weeks

Recommended Dosage in Adults: The recommended dosage in adults is one tablet (400mg sofosbuvir and 100mg velpatasvir) taken orally once daily with or without food.
When administered the recommended dosage of ribavirin is based on weight (administered with food): 1,000mg per day for patients less than 75kg and 1,200mg for those weighing at least 75kg, divided and administered twice daily. The starting dosage and on-treatment dosage of ribavirin can be decreased based on hemoglobin and creatinine clearance. For ribavirin dosage modifications refer to the ribavirin prescribing information. ***Recommended Dosage in Paediatric Patients 6 Years of Age and Older or Weighing at Least 17kg:*** The recommended dosage in paediatric patients 6 years of age and older or weighing at least 17kg is based on weight and provided in Table 2. Table 3 provides the weight-based dosage of ribavirin when used in combination for paediatric patients. Take once daily with or without food.

Table 2: Dosing for Paediatric Patients 6 Years and Older or Weighing at least17 kg with Genotype 1, 2, 3, 4, 5, or 6 HCV

Body Weight (kg)	Dosing of **OCVIR®-V**	**OCVIR®-V** Daily Dose
At least 30	One 400mg/100mg tablet once daily **or** Two 200mg/50mg tablets once daily	400mg/100mg per day
17 to less than 30	One 200mg/50mg tablet once daily	200mg/50mg per day

Table 3: Recommended Dosing for Ribavirin in Combination Therapy for Paediatric Patients 6 Years and Older

Body Weight (kg)	Oral Ribavirin Daily Dosage
Less than 47	15mg per kg per day (divided dose AM & PM)
47–49	600mg per day (1 x 200mg AM, 2 x 200mg PM)
50–65	800mg per day (2 x 200mg AM, 2 x 200mg PM)
66–80	1,000mg per day (2 x 200mg AM, 3 x 200mg PM)
Greater than 80	1,200 mg per day (3 x 200mg AM, 3 x 200mg PM)

The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food

Renal Impairment: No dosage adjustment is recommended in patients with any degree of renal impairment, including patients requiring dialysis. Administer with or without ribavirin according to the recommendations in Table 1. Refer to ribavirin tablet prescribing information for ribavirin dosage modification for patients with CrCl less than or equal to 50mL per minute.

Hepatic Impairment: No dose adjustment of **OCVIR®-V** is required for patients with mild, moderate, or severe hepatic impairment. **Elderly patients:** No dose adjustment is warranted for elderly patients. **Method of Administration:** For oral use. Patients should be instructed to swallow the tablet whole with or without food. Due to the bitter taste, it is recommended that the film coated tablet is not chewed or crushed.

CONTRAINDICATIONS:
- **OCVIR®-V** and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated.
- Hypersensitivity to the active substances or to any of the excipients.
- Medicinal products that are strong P-glycoprotein (P-gp) and/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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE: 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 **OCVIR®-V** 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 co-administration, 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. 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. **Renal impairment:** Safety data are limited in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) and ESRD requiring haemodialysis. **OCVIR®-V** can be used in these patients with no dose adjustment when no other relevant treatment options are available. When **OCVIR®-V** is used in combination with ribavirin refer also to the Summary of Product Characteristics for ribavirin for patients with creatinine clearance < 50 mL/min. **Use with moderate P-gp inducers 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. Co-administration of such medicinal products with **OCVIR®-V** is not recommended. **Use with certain HIV antiretroviral regimens:** Sofosbuvir / velpatasvir has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). Patients receiving sofosbuvir plus velpatasvir concomitantly with elvitegravir/cobicistat/emtricitabine /tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. **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 **OCVIR®-V** has not been assessed in patients with CPT Class C cirrhosis. **Liver transplant patients:** The safety and efficacy in the treatment of HCV infection in patients who are post-liver transplant has not been assessed. Treatment in accordance with the recommended posology should be guided by an assessment of the potential benefits and risks for the individual patient.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: As **OCVIR®-V** contains sofosbuvir and velpatasvir, any interactions that have been identified with these active substances individually may occur with **OCVIR®-V**.
Potential 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 **OCVIR®-V** with medicinal products that are substrates of these transporters may increase the exposure of such medicinal products.
Potential for other medicinal products to affect OCV: 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 and/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 is contraindicated. Medicinal products that are moderate P-gp inducers and/or moderate CYP inducers (e.g. efavirenz, modafinil, oxcarbazepine or rifapentine) may decrease sofosbuvir or velpatasvir plasma concentration leading to reduced therapeutic effect. Co-administration with such medicinal products is not recommended.
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 mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; may be co-administered with P-gp, BCRP, OATP and CYP inhibitors.
Patients treated with vitamin K antagonists: As liver function may change during treatment with sofosbuvir / velpatasvir, a close monitoring of International Normalised Ratio (INR) values is recommended. **Impact of DAA therapy on drugs metabolized by the liver:** The pharmacokinetics of drugs that are metabolized by the liver (e.g. immune suppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

INTERACTIONS BETWEEN OCVIR®-V AND OTHER MEDICINAL PRODUCTS:

Medicinal product by therapeutic areas / Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval)a,b				Recommendation concerning co-administration with Sofosbuvir / Velpatasvir
	Active	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 / velpatasvir administration by 4 hours.
H2-receptor antagonists					
Famotidine (40mg single dose)/ sofosbuvir / velpatasvir (400 / 100mg single dose). Famotidine dosed simultaneously with sofosbuvir / velpatasvir, Cimetidine, Nizatidine, Ranitidine (Increase in gastric pH)	Sofosbuvir	↔	↔		H2-receptor antagonists may be administered simultaneously with or staggered from sofosbuvir / velpatasvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily.
	Velpatasvir	↓ 0.80 (0.70, 0.91)	↓ 0.81 (0.71, 0.91)		
Famotidine (40mg single dose)/ sofosbuvir / velpatasvir (400 / 100mg single dose)c	Sofosbuvir	↓ 0.77 (0.68, 0.87)	↓ 0.80 (0.73, 0.88)		
Famotidine dosed 12 hours prior to sofosbuvir / velpatasvir d (Increase in gastric pH)	Velpatasvir	↔	↔		
Proton pump inhibitors					
Omeprazole (20mg once daily)/ sofosbuvir / velpatasvir (400 / 100mg single dose fasted)c	Sofosbuvir	↓ 0.66 (0.55, 0.78)	↓ 0.71 (0.60, 0.83)		Co-administration with proton pump inhibitors is not recommended. If it is considered necessary to co-administer, then sofosbuvir / velpatasvir should be administered with food and taken 4 hours before proton pump inhibitor at max doses comparable to omeprazole 20mg.
Omeprazole dosed simultaneously with sofosbuvir / velpatasvir Lansoprazole, Rabeprazole, Pantoprazole, Esomeprazole (Increase in gastric pH)	Velpatasvir	↓ 0.63 (0.50, 0.78)	↓ 0.64 (0.52, 0.79)		
Omeprazole(20mg once daily)/ sofosbuvir / velpatasvir (400 / 100mg single dose fed)c	Sofosbuvir	↓ 0.79 (0.68, 0.92)	↔		
Omeprazole dosed 4 hours after sofosbuvir / velpatasvir (Increase in gastric pH)	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 / velpatasvir.
Digoxin	Interaction only studied with velpatasvir Expected: ↔ Sofosbuvir				Co-administration of sofosbuvir / velpatasvir with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with sofosbuvir / velpatasvir.
Digoxin (0.25mg single dose)f / velpatasvir (100mg single dose) (Inhibition of P-gp)	Effect on velpatasvir exposure not studied Expected: ↔ Velpatasvir				
	Observed: Digoxin	↑ 1.9 (1.7, 2.1)	↑ 1.3 (1.1, 1.6)		
ANTICOAGULANTS					
Dabigatran etexilate (Inhibition of P-gp)	Interaction not studied. Expected: ↑ Dabigatran ↔ Sofosbuvir ↔ Velpatasvir				Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with sofosbuvir / velpatasvir. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.
Vitamin K antagonists	Interaction not studied				Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with sofosbuvir / velpatasvir .
ANTICONVULSANTS					
Phenytoin, Phenobarbital (Induction of P-gp CYPs)	Interaction not studied. Expected: ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir / velpatasvir is contraindicated with phenobarbital and phenytoin.
Carbamazepine (Induction of P-gp and CYPs)	Interaction not studied. Expected: ↓ Velpatasvir				Sofosbuvir / velpatasvir is contraindicated with carbamazepine.
	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 / velpatasvir with oxcarbazepine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of sofosbuvir / velpatasvir . Co-administration is not recommended.
ANTIFUNGALS					
Ketoconazole	Interaction only studied with velpatasvir Expected: ↔ Sofosbuvir				No dose adjustment of sofosbuvir / velpatasvir or ketoconazole is required.
Ketoconazole (200mg twice daily)/ velpatasvir (100mg 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)		
ANTIMYCOBACTERIALS					
Rifampicin (600mg once daily) / sofosbuvir (400mg single dose)d (Induction of P-gp and CYPs)	Effect on rifampicin exposure not studied. Expected: ↔ Rifampicin				Sofosbuvir / velpatasvir is contraindicated with rifampicin.
	Observed: Sofosbuvir	↓ 0.23 (0.19, 0.29)	↓ 0.28 (0.24, 0.32)		
Rifampicin (600mg once daily)/ velpatasvir (100mg 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 / velpatasvir is contraindicated with rifabutin.
	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 / velpatasvir with rifapentine is expected to decrease the concentration of sofosbuvir and velpatasvir, leading to reduced therapeutic effect of sofosbuvir / velpatasvir. Co-administration is not recommended.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS					
Tenofovir disoproxil fumarate	Sofosbuvir / velpatasvir has been shown to increase tenofovir exposure (P-gp-inhibition). The increase in tenofovir exposure (AUC and C_{max}) was around 40-80% during co-treatment with sofosbuvir / velpatasvir and tenofovir disoproxil fumarate / emtricitabine as part of various HIV regimens. Patients receiving tenofovir disoproxil fumarate and sofosbuvir / velpatasvir concomitantly should be monitored for adverse reactions associated with tenofovir disoproxil fumarate. Refer to the tenofovir disoproxil fumarate-containing product's Summary of Product Characteristics for recommendations on renal monitoring.				

Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600/ 200/ 300mg once daily)/ sofosbuvir / velpatasvir (400 / 100mg once daily)c, d	Efavirenz	↔	↔	↔	Co-administration of sofosbuvir / velpatasvir with efavirenz/ emtricitabine / tenofovir disoproxil fumarate is expected to decrease the concentration of velpatasvir. Co-administration of sofosbuvir / velpatasvir with efavirenz-containing regimens is not recommended.
	Sofosbuvir	↑ 1.4 (1.1, 1.7)	↔		
	Velpatasvir	↓ 0.53 (0.43, 0.64)	↓ 0.47 (0.39, 0.57)	↓ 0.43 (0.36, 0.52)	
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate (200/ 25/ 300mg once daily)/ sofosbuvir / velpatasvir (400/ 100mg once daily)c, d	Rilpivirine	↔	↔	↔	No dose adjustment of sofosbuvir / velpatasvir or emtricitabine / rilpivirine / tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS					
Atazanavir boosted with ritonavir (300 / 100mg once daily) + emtricitabine / tenofovir disoproxil fumarate (200 / 300mg once daily)/ sofosbuvir / velpatasvir (400 / 100mg once daily)c, d	Atazanavir	↔	↔	↑ 1.4 (1.2, 1.6)	No dose adjustment of sofosbuvir / velpatasvir, atazanavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔		↑ 1.3 (1.5, 1.4)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↑ 1.6 (1.4, 1.7)	↑ 2.4 (2.2, 2.6)	↑ 4.0 (3.6, 4.5)	
Darunavir boosted with ritonavir (800 / 100mg once daily) + emtricitabine / tenofovir disoproxil fumarate (200/ 300mg once daily) / sofosbuvir / velpatasvir (400 / 100mg once daily)c, d	Darunavir	↔	↔	↔	No dose adjustment of sofosbuvir / velpatasvir, darunavir (ritonavir boosted) or emtricitabine / tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.62 (0.54, 0.71)	↓ 0.72 (0.66, 0.80)		
	Velpatasvir	↓ 0.76 (0.65, 0.89)	↔	↔	
Lopinavir boosted with ritonavir (4 x 200mg/ 50mg once daily) + emtricitabine / tenofovir disoproxil fumarate (200 / 300mg once daily) / sofosbuvir / velpatasvir (400 / 100mg once daily)c, d	Lopinavir	↔	↔	↔	No dose adjustment of sofosbuvir / velpatasvir, lopinavir (ritonavir boosted) or emtricitabine / tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.59 (0.49, 0.71)	↓ 0.7 (0.6, 0.8)		
	Velpatasvir	↓ 0.70 (0.59, 0.83)	↔	↑1.6 (1.4, 1.9)	
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400mg twice daily)g + emtricitabine / tenofovir disoproxil fumarate (200 / 300mg once daily)/ sofosbuvir / velpatasvir (400 / 100mg once daily)c, d	Raltegravir	↔	↔	↓ 0.79 (0.42, 1.5)	No dose adjustment of sofosbuvir / velpatasvir, raltegravir or emtricitabine / tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate (150 / 150 / 200 / 10mg once daily)/ sofosbuvir / velpatasvir (400 / 100mg once daily)c, d	Elvitegravir	↔	↔	↔	No dose adjustment of sofosbuvir / velpatasvir or elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide fumarate is required.
	Cobicistat	↔	↔	↑ 2.0 (1.7, 2.5)	
	Tenofovir alafenamide	↔	↔		
	Sofosbuvir	↔	↑ 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/ 300mg once daily)/ sofosbuvir / velpatasvir (400 / 100mg once daily)c, d	Elvitegravir	↔	↔	↔	No dose adjustment of sofosbuvir / velpatasvir or elvitegravir/ cobicistat / emtricitabine / tenofovir disoproxil fumarate is required.
	Cobicistat	↔	↔	↑ 1.7 (1.5, 1.9)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↑ 1.4 (1.2, 1.5)	
Dolutegravir (50mg once daily) / sofosbuvir / velpatasvir (400 / 100mg once daily)	Dolutegravir	↔	↔	↔	No dose adjustment of sofosbuvir / velpatasvir or dolutegravir is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
HERBAL SUPPLEMENTS					
St. John's wort (Induction of P-gp and CYPs)	Interaction not studied. Expected: ↓ Sofosbuvir ↓ Velpatasvir				Sofosbuvir / velpatasvir is contraindicated with St. John's wort.
HMG-CoA REDUCTASE INHIBITORS					
Atorvastatin (40mg single dose) + sofosbuvir / velpatasvir (400 / 100mg once daily)d	Observed: Atorvastatin	↑ 1.7 (1.5, 1.9)	↑ 1.5 (1.5, 1.6)		No dose adjustment of sofosbuvir / velpatasvir or atorvastatin is required.
Rosuvastatin	Interaction only studied with velpatasvir Expected: ↔ Sofosbuvir				Co-administration of sofosbuvir / velpatasvir with rosuvastatin increases the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin, at a dose that does not exceed 10mg, may be administered with sofosbuvir / velpatasvir .
Rosuvastatin (10mg single dose) / velpatasvir (100mg once daily)d (Inhibition of OATP1B and BCRP)	Observed: Rosuvastatin	↑ 2.6 (2.3, 2.9)	↑ 2.7 (2.5, 2.9)		
	Effect on velpatasvir exposure not studied Expected: ↔ Velpatasvir				
Pravastatin	Interaction only studied with velpatasvir Expected: ↔ Sofosbuvir				No dose adjustment of sofosbuvir / velpatasvir or pravastatin is required.
Pravastatin (40mg single dose) / velpatasvir (100mg once daily)d (Inhibition of OATP1B)	Observed: Pravastatin	↑ 1.3 (1.1, 1.5)	↑ 1.4 (1.2, 1.5)		
	Effect on velpatasvir exposure not studied Expected: ↔ Velpatasvir				
Other statins	Expected: ↑ Statins				Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with sofosbuvir / velpatasvir , careful monitoring for statin adverse reactions should be undertaken and a reduced dose of statins should be considered if required.
NARCOTIC ANALGESICS					
Methadone (Methadone maintenance therapy [30 to 130mg daily]) / sofosbuvir (400mg once daily)d	R-methadone	↔	↔	↔	No dose adjustment of sofosbuvir / velpatasvir or methadone is required.
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.3 (1.0, 1.7)		
Methadone	Interaction only studied with sofosbuvir Expected: ↔ Velpatasvir				
IMMUNOSUPPRESSANTS					
Cyclosporin (600mg single dose) / sofosbuvir (400mg single dose)f	Cyclosporin	↔	↔		No dose adjustment of sofosbuvir / velpatasvir or cyclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of cyclosporin may be required.
	Sofosbuvir	↑ 2.5 (1.9, 3.5)	↑ 4.5 (3.3, 6.3)		
Cyclosporin (600mg single dose)f / velpatasvir (100mg single dose)d	Cyclosporin	↔	↓ 0.88 (0.78, 1.0)		
	Velpatasvir	↑ 1.6 (1.2, 2.0)	↑ 2.0 (1.5, 2.7)		

Tacrolimus (5mg single dose)f / sofosbuvir (400mg single dose)d	Tacrolimus	↓ 0.73 (0.59, 0.90)	↑ 1.1 (0.84, 1.4)		No dose adjustment of sofosbuvir / velpatasvir or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
	Sofosbuvir	↓ 0.97 (0.65, 1.4)	↑ 1.1 (0.81, 1.6)		
Tacrolimus	Effect on velpatasvir exposure not studied. Expected: ↔ Velpatasvir				
ORAL CONTRACEPTIVES					
Norgestimate / ethinyl estradiol (norgestimate 0.180mg / 0.215mg/ 0.25 mg/ ethinyl estradiol 0.025 mg) / sofosbuvir (400mg once daily)d	Norel-gestromin	↔	↔	↔	No dose adjustment of oral contraceptives is required.
	Norgestrel	↔	↑ 1.2 (0.98, 1.5)	↑ 1.2 (1.0, 1.5)	
	Ethinyl estradiol	↔	↔	↔	
Norgestimate / ethinyl estradiol (norgestimate 0.180mg / 0.215mg / 0.25mg / ethinyl estradiol 0.025mg) / velpatasvir (100mg once daily)d	Norel-gestromin	↔	↔	↔	
	Norgestrel	↔	↔	↔	
	Ethinyl estradiol	↑ 1.4 (1.2, 1.7)	↔	↓ 0.83 (0.65, 1.1)	

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00. b. All interaction studies conducted in healthy volunteers.
c. Administered as sofosbuvir / velpatasvir. d. Lack of pharmacokinetics interaction bounds 70-143%. e. These are medicinal products within class where similar interactions could be predicted.
f. Bioequivalence / Equivalence boundary 80-125%. g. Lack of pharmacokinetics interaction bounds 50-200%

FERTILITY, PREGNANCY AND LACTATION: Fertility: No human data on the effect of sofosbuvir / velpatasvir on fertility are available. Animal studies do not indicate harmful effects of sofosbuvir or velpatasvir on fertility. If ribavirin is co-administered with sofosbuvir / velpatasvir , refer to the Summary of Product Characteristics for ribavirin for detailed recommendations regarding pregnancy, contraception, and breast-feeding. **Pregnancy**: There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir / velpatasvir in pregnant women. **Sofosbuvir**: Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. It has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose. **Velpatasvir**: Animal studies have shown a possible link to reproductive toxicity. As a precautionary measure, sofosbuvir / velpatasvir use is not recommended during pregnancy. **Breast-feeding: It** is unknown whether sofosbuvir, metabolites of sofosbuvir or velpatasvir are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of velpatasvir and metabolites of sofosbuvir in milk. A risk to the newborns/infants cannot be excluded. Therefore, sofosbuvir / velpatasvir should not be used during breast-feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Sofosbuvir / velpatasvir has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS: 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. **Tabulated summary of adverse reactions:** Assessment of adverse reactions for sofosbuvir / velpatasvir is based on safety data from clinical studies and postmarketing experience. All adverse reactions are presented in below table.

Frequency	Adverse drug reaction
Skin and subcutaneous tissue disorders:	
Common	rash
Uncommon	angioedema

Adverse reaction identified through post-marketing surveillance for sofosbuvir / velpatasvir-containing products

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 10g/dL and 8.5g/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. 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 selected 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. ● Skin disorders: Frequency not known: Stevens-Johnson syndrome.

OVERDOSE: The highest documented doses of sofosbuvir and velpatasvir were a single dose of 1,200mg and a single dose of 500mg, respectively. The effects of higher doses/exposures are not known.
No specific antidote is available for overdose with sofosbuvir / velpatasvir. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with sofosbuvir / velpatasvir consists of general supportive measures including monitoring of vital signs, as well as observation of the clinical status of the patient. Haemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Haemodialysis is unlikely to result in significant removal of velpatasvir, since velpatasvir is highly bound to plasma protein.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES: Therapeutic classification: 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. **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.
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 / velpatasvir, sofosbuvir was absorbed quickly and the peak median plasma concentration was observed 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed 3 hours post-dose. Velpatasvir median peak concentrations were observed at 3 hours post-dose. **Effects of food:** Relative to fasting conditions, the administration of a single dose of sofosbuvir / velpatasvir with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal resulted in a 34% and 21% increase in velpatasvir $AUC^{0\text{-}inf}$, 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}. **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 400mg 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 100mg 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. After a single 400mg 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 100mg [^{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 400mg 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 / velpatasvir were 0.5 and 25 hours, respectively. Following a single 100mg oral dose of [^{14}C]-velpatasvir, mean total recovery of the [^{14}C]-radioactivity was 95%, consisting of approximately 94% and 0.4% recovered from the feces and urine, respectively. Unchanged velpatasvir was the major species in feces accounting for a mean of 77% of the administered dose, followed by monohydroxylated velpatasvir (5.9%) and desmethylated velpatasvir (3.0%). These data indicate that biliary excretion of parent drug was a major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of sofosbuvir / velpatasvir was approximately 15 hours. **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 m^2) moderate (eGFR ≥30 and < 50 mL/min/1.73 m m^2) severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and patients with ESRD requiring haemodialysis following a single 400mg dose of sofosbuvir, relative to patients with normal renal function (eGFR > 80 mL/min/1.73 m^2). GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400mg dose of sofosbuvir, a 4 hour haemodialysis removed 18% of administered dose. The pharmacokinetics of velpatasvir was studied with a single dose of 100mg velpatasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). **Hepatic impairment:** The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400mg 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 100mg velpatasvir in HCV negative patients with moderate and severe hepatic impairment (CPT Class B and C). Compared to subjects with normal hepatic function velpatasvir total plasma exposure (AUC^{inf}) was similar in patients with moderate or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure to velpatasvir. **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.

STABILITY

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AVAILABILITY

OCVIR®-V 400mg / 100mg tablets in a pack of 28's

INSTRUCTIONS

Dosage as advised by the physician. To be sold on the prescription of registered medical practitioner.
Keep out of reach of children. Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine. Store in the original package in order to protect from moisture.

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