160 mm

520 mm

To be sold by retail on the prescription of gastroenterologist only

PRESCRIBING INFORMATION

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Sofosbuvir 400 mg and Velpatasvir 100 mg Tablets IP

VELPAGEN

For India Only

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 Sofosbuvir 400 mg and Velpatasvir 100 mg Tablets. 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.

1. Generic Name
Sofosbuvir 400 mg & Velpatasvir 100 mg Tablets IP

2. Qualitative and Quantitative Composition
Each film coated tablet contains:
Sofosbuvir IP 400 mg
Velpatasvir IP 100 mg
Excipients q.s
Colours: Indigo Carmine Aluminum Lake, Brilliant Blue FCF Aluminum Lake & Titanium Dioxide IP

3. DOSAGE FORM & STRENGTH
400 mg sofosbuvir and 100 mg velpatasvir film coated Tablet for oral use

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Sofosbuvir and velpatasvir is indicated for the treatment of adult patients with chronic Hepatitis C virus Genotype 1, 2, 3, 4, 5 or 6 infection:
- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with Ribavirin

4.2 Dosage and Administration
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 with Sofosbuvir and Velpatasvir. Sofosbuvir/velpatasvir treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Recommended Treatment Regimen and Duration in Patients 3 Years of Age and Older
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 EPCLUSA once daily for 12 weeks.

Table 1 Recommended Treatment Regimen and Duration in Patients 3 Years of Age and Older with Genotype 1, 2, 3, 4, 5, or 6 HCV

Patient Population	Treatment Regimen and Duration
Treatment-naïve and treatment-experienced[a], without cirrhosis and with compensated cirrhosis (Child-Pugh A)	Sofosbuvir + Velpatasvir for 12 weeks
Treatment-naïve and treatment-experienced[a], with decompensated cirrhosis (Child-Pugh B or C)	Sofosbuvir + Velpatasvir + ribavirin[b] 12 weeks

a. In clinical trials in adults, regimens contained peginterferon alfa/ribavirin with or without an HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir).
b. See ribavirin dosage recommendations.

Recommended Dosage in Adults
The recommended dosage of Sofosbuvir + Velpatasvir in adults is one tablet (400 mg sofosbuvir and 100 mg velpatasvir) taken orally once daily with or without food.
When administered with Sofosbuvir + Velpatasvir, the recommended dosage of ribavirin is based on weight (administered with food): 1,000 mg per day for patients less than 75 kg and 1,200 mg for those weighing at least 75 kg, 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 Pediatric Patients 3 Years of Age and Older
The recommended dosage of Sofosbuvir + Velpatasvir in pediatric patients 3 years of age and older is based on weight and provided in Table 2. Table 3 provides the weight-based dosage of ribavirin when used in combination with Sofosbuvir + Velpatasvir for pediatric patients. Take Sofosbuvir + Velpatasvir oral pellets or tablets once daily with or without food. In pediatric patients less than 6 years of age, administer the oral pellets with food to increase tolerability related to palatability.

Table 2 Dosing for Pediatric Patients 3 Years and Older with Genotype 1, 2, 3, 4, 5, or 6 HCV Using Sofosbuvir + Velpatasvir Oral Pellets or Tablets

Body Weight (kg)	Sofosbuvir + Velpatasvir Daily Dose	Dosing of Sofosbuvir + Velpatasvir Oral Pellets	Dosing of Sofosbuvir + Velpatasvir Tablet
less than 17	150 mg/37.5 mg per day	one 150 mg/37.5 mg packet of pellets once daily	N/A
17 to less than 30	200 mg/50 mg per day	one 200 mg/50 mg packet of pellets once daily	one 200 mg/50 mg tablet once daily
at least 30	400 mg/100 mg per day	two 200 mg/50 mg packets of pellets once daily	one 400 mg/100 mg tablet once daily[a]

a. Two 200 mg/50 mg tablets once daily can be used for patients who cannot swallow the 400 mg/100 mg tablet.

Table 3 Recommended Dosing for Ribavirin in Combination Therapy with Sofosbuvir + Velpatasvir for Pediatric Patients 3 Years and Older

Body Weight (kg)	Oral Ribavirin Daily Dosage[a]
less than 47	15 mg per kg per day (divided dose AM and PM)
47–49	600 mg per day (1 x 200 mg AM, 2 x 200 mg PM)
50–65	800 mg per day (2 x 200 mg AM, 2 x 200 mg PM)
66–80	1,000 mg per day (2 x 200 mg AM, 3 x 200 mg PM)
greater than 80	1,200 mg per day (3 x 200 mg AM, 3 x 200 mg PM)

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

Renal Impairment
No dosage adjustment of Sofosbuvir + Velpatasvir is recommended in patients with any degree of renal impairment, including patients requiring dialysis. Administer Sofosbuvir and Velpatasvir 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 50 mL per minute

4.3 Contraindications
Hypersensitivity to the sofosbuvir or velpatasvir or to any of the excipients of the product.

Use with potent P-gp and potent CYP inducers
Medicinal products that are potent P-glycoprotein (P-gp) or potent cytochrome P_{450} (CYP) inducers (rifampicin, rifabutin, St. John's wort [Hypericum perforatum], carbamazepine, phenobarbital and phenytoin). Co-administration will significantly decrease sofosbuvir or velpatasvir plasma concentrations and could result in loss of efficacy of sofosbuvir and velpatasvir.

4.4 Special warnings and precautions for use
Sofosbuvir and velpatasvir 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 used in combination with amiodarone. Bradycardia has generally occurred within hours to days, but c ases 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 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.
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.

Patients who have previously failed therapy with an NS5A-containing regimen
There are no clinical data to support the efficacy of sofosbuvir and velpatasvir for the treatment of patients who have failed treatment with a regimen containing another NS5A inhibitor. However, on the basis of NS5A resistance associated variants (RAVs) typically seen in patients who have failed therapy with other NS5A inhibitor containing regimens, the in vitro pharmacology of velpatasvir, and the outcomes of sofosbuvir and velpatasvir treatment in NS5A-naïve patients with baseline NS5A RAVs enrolled into the clinical studies, treatment with sofosbuvir + velpatasvir + Ribavirin 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.

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

Use with certain HIV antiretroviral regimens
Sofosbuvir and velpatasvir has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of sofosbuvir/velpatasvir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of sofosbuvir and velpatasvir with the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving sofosbuvir and 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.

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

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

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

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/velpatasvir can be used in these patients with no dose adjustment when no other relevant treatment options are available. When Sofosbuvir/velpatasvir is used in combination with ribavirin, for patients with creatinine clearance < 50 mL/min.

4.5 Drug Interactions
Potential for other drugs to affect sofosbuvir and velpatasvir
Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. *In vitro*, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of sofosbuvir and velpatasvir. The use of these agents with sofosbuvir and velpatasvir is not recommended. Sofosbuvir and velpatasvir may be coadministered with P-gp, BCRP, and CYP inhibitors.

Potential for sofosbuvir and velpatasvir to affect other drugs
Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. Coadministration of sofosbuvir and velpatasvir with drugs that are substrates of these transporters may increase the exposure of such drugs.

Patients treated with vitamin K antagonists
As liver function may change during treatment with sofosbuvir and velpatasvir, a close monitoring of International Normalised Ratio (INR) values is recommended.

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/velpatasvir and other medicinal products
Interactions 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.

Established and potentially significant drug interactions
The drug interactions described are based on studies conducted with either sofosbuvir/velpatasvir, interactions that may occur with sofosbuvir and velpatasvir.

Interactions between Sofosbuvir/velpatasvir and other medicinal products

Medicinal product by therapeutic areas/ Possible Mechanism of Interaction	Effects on medicinal product levels. Mean ratio (90% confidence interval)[a,b]				Recommendation concerning co-administration with Sofosbuvir/velpatasvir
	Active	C_{max}	AUC	C_{min}	
ACID REDUCING AGENTS:					
					Velpatasvir solubility decreases as pH increases. Medicinal products that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids					
e.g. Aluminium or magnesium calcium carbonate (Increase in gastric pH)	Interaction not studied. *Expected.* ↔ Sofosbuvir ↓ Velpatasvir				It is recommended to separate antacid and Sofosbuvir/velpatasvir administration by 4 hours.
H2-receptor antagonists					
Famotidine (40 mg single dose)/ sofosbuvir/velpatasvir (400/100 mg single dose)[c] Famotidine dosed simultaneously with Sofosbuvir/velpatasvird Cimetidine[e] Nizatidine[e] Ranitidine[e] (Increase in gastric pH)	Sofosbuvir	↔	↔		H_2-receptor antagonists may be administered simultaneously with or staggered from Sofosbuvir/velpatasvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
	Velpatasvir	↓ 0.80 (0.70, 0.91)	↓ 0.81 (0.71, 0.91		
Famotidine (40 mg single dose)/ sofosbuvir/ velpatasvir (400/100 mg single dose)[c] Famotidine dosed 12 hours prior to Sofosbuvir/velpatasvird (Increase in gastric pH)	Sofosbuvir	↓ 0.77 (0.68, 0.87)	↓ 0.80 (0.73, 0.88)		
	Velpatasvir	↔	↔		
Proton pump inhibitors					
Omeprazole (20 mg once daily)/ sofosbuvir/velpatasvir (400/ 100 mg single dose fasted)[c] Omeprazole dosed simultaneously with Sofosbuvir/velpatasvird Lansoprazole[e] Rabeprazole[e] Pantoprazole[e] Esomeprazole[e] (Increase in gastric pH)	Sofosbuvir	↓ 0.66 (0.55, 0.78)	↓ 0.71 (0.60, 0.83)		Co-administration with proton pump inhibitors is not recommended. If it is considered necessary to coadminister, then Sofosbuvir/velpatasvir should be administered with food and taken 4 hours before proton pump inhibitor at max doses comparable to omeprazole 20 mg.
	Velpatasvir	↓ 0.63 (0.50, 0.78)	↓ 0.64 (0.52, 0.79)		
Omeprazole (20 mg once daily)/ sofosbuvir/velpatasvir (400/ 100 mg single dose fed)[c] Omeprazole dosed 4 hours after Sofosbuvir/ velpatasvir[d] (Increase in gastric pH)	Sofosbuvir	↓ 0.79 (0.68, 0.92)	↔		
	Velpatasvir	↓ 0.67 (0.58, 0.78)	↓ 0.74 (0.63, 0.86)		
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 (0.25 mg single dose)f/velpatasvir (100 mg single dose) (Inhibition of P-gp)	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
	Observed: Digoxin	↑ 1.9 (1.7, 2.1)	↑ 1.3 (1.1, 1.6)		
ANTICOAGULANTS					
Dabigatran etexilate (Inhibition of P-gp)	Interaction not studied. *Expected:* ↑ Dabigatran ↔ Sofosbuvir ↔ Velpatasvir				Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with Sofosbuvir/velpatasvir. A coagulation test helps to identify patients with an increased bleeding 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 and 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)		Sofosbuvir/velpatasvir is contraindicated with carbamazepine
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 (200 mg twice daily)/ velpatasvir (100 mg single dose)[d] (Inhibition of P-gp and CYPs) Itraconazolee 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/velpatasvir is contraindicated with rifampicin
	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				
	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. Coadministration 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.				
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600/ 200/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Efavirenz	↔	↔	↔	Co-administration of Sofosbuvir/velpatasvir with efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is expected to decrease the concentration of velpatasvir. Co-administration of Sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.
	Sofosbuvir	↑ 1.4 (1.1, 1.7)	↔		
	Velpatasvir	↓ 0.53 (0.43, 0.64)	↓ 0.47 (0.39, 0.57)	↓ 0.43 (0.36, 0.52)	
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate (200/ 25/ 300 mg once daily)/ sofosbuvir/ velpatasvir (400/100 mg once daily)[c,d]	Rilpivirine	↔	↔	↔	No dose adjustment of Sofosbuvir/velpatasvir or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔	↔	
	Velpatasvir	↔	↔	↔	
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS					
Atazanavir boosted with ritonavir (300/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Atazanavir	↔	↔	↑ 1.4 (1.2,1.6)	No dose adjustment of Sofosbuvir/velpatasvir, atazanavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔		↑ 1.3 (1.5, 1.4)	
	Sofosbuvir	↔	↔		
	Velpatasvir	↑ 1.6 (1.4, 1.7)	↑ 2.4 (2.2, 2.6)	↑ 4.0 (3.6, 4.5)	
Darunavir boosted with ritonavir (800/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Darunavir	↔	↔	↔	No dose adjustment of Sofosbuvir/velpatasvir, darunavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.62 (0.54, 0.71)	↓ 0.72 (0.66, 0.80)		
	Velpatasvir	↓ 0.76 (0.65, 0.89)	↔	↔	
Lopinavir boosted with ritonavir (4x200 mg/ 50 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Lopinavir	↔	↔	↔	No dose adjustment of Sofosbuvir/velpatasvir, lopinavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Ritonavir	↔	↔	↔	
	Sofosbuvir	↓ 0.59 (0.49 0.71)	↓ 0.7 (0.6, 0.8)		
	Velpatasvir	↓ 0.70 (0.59, 0.83)	↔	↑ 1.6 (1.4, 1.9)	
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS					
Raltegravir (400 mg twice daily)g + emtricitabine/ tenofovir disoproxil fumarate (200/ 300 mg once daily)/sofosbuvir/ velpatasvir (400/100 mg once daily)[c, d]	Raltegravir	↔	↔	↓ 0.79 (0.42, 1.5)	No dose adjustment of Sofosbuvir/velpatasvir, raltegravir or emtricitabine/ tenofovir disoproxil fumarate is required.
	Sofosbuvir	↔	↔		
	Velpatasvir	↔	↔	↔	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate (150/ 150/ 200/ 10 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Elvitegravir	↔	↔	↔	No dose adjustment of Sofosbuvir/velpatasvir, darunavir (ritonavir boosted) or emtricitabine/ tenofovir disoproxil fumarate is required.
	Cobicistat	↔	↔	↑ 2.0 (1.7, 2.5)	
	Tenofovir alafenamide	↔	↔		
	Sofosbuvir	↔	↑ 1.4 (1.2, 1.5)		
	Velpatasvir	↑ 1.3 (1.2, 1.5)	↑ 1.5 (1.4, 1.7)	↑ 1.6 (1.4, 1.8)	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (150/ 150/ 200/ 300 mg once daily)/sofosbuvir/ velpatasvir (400/ 100 mg once daily)[c, d]	Elvitegravir	↔	↔	↔	No dose adjustment of Sofosbuvir/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 (50 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg once daily)	Dolutegravir	↔	↔	↔	No dose adjustment of Sofosbuvir/velpatasvir or dolutegravir is required.
	Sofosbuvir	↔	↔	↔	
	Velpatasvir	↔	↔	↔	

Front

Colour: Black
Spec.: 41± 15% Gsm Bible Paper
Dimension: 160x520 mm
Fold Size: 40x65 mm
Reason for change: Artwork revised as per IP addendum 2024

160 mm

520 mm

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 (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/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 10 mg, may be administered with Sofosbuvir/velpatasvir.
Rosuvastatin (10 mg single dose)/ velpatasvir (100 mg once daily)[d] (Inhibition of OATP1 and BCRP)	*Observed:* Rosuvastatin	↑ 2.6 (2.3, 2.9)	↑ 2.7 (2.5, 2.9)		
	Effect on velpatasvir exposure not studied *Expected:* ↔ Velpatasvir				
Pravastatin	Interaction only studied with velpatasvir *Expected:* ↔ Sofosbuvir				No dose adjustment of Sofosbuvir/velpatasvir or pravastatin is required.
Pravastatin (40 mg single dose)/ velpatasvir (100 mg once daily)[d] (Inhibition of OATP1B)	*Observed:* Velpatasvir	↑ 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 130 mg daily])/ sofosbuvir (400 mg once daily)[d]	R-methadone	↔	↔	↔	No dose adjustment of Sofosbuvir/velpatasvir or methadone is required.
	S-methadone	↔	↔	↔	
	Sofosbuvir	↔	↑ 1.3 (1.0, 1.7)		
Methadone	Interaction only studied with sofosbuvir *Expected:* ↔ Velpatasvir				
IMMUNOSUPPRESSANTS					
Ciclosporin (600 mg single dose)/ sofosbuvir (400 mg single dose)[f]	Ciclosporin	↔	↔		No dose adjustment of Sofosbuvir/velpatasvir or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
	Sofosbuvir	↑ 2.5 (1.9, 3.5)	↑ 4.5 (3.3, 6.3)		
Ciclosporin (600 mg single dose)[f]/ velpatasvir (100 mg single dose)[d]	Ciclosporin	↔	↓ 0.88 (0.7, 1.0)		
	Velpatasvir	↑ 1.6 (1.2, 2.0)	↑ 2.0 (1.5, 2.7)		
Tacrolimus (5 mg single dose)[f]/ sofosbuvir (400 mg single dose)[d]	Tacrolimus	↓ 0.73 (0.59, 0.90)	↑ 1.1 (0.84, 1.4)		No dose adjustment of Sofosbuvir/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 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily)[d]	Norelgestromin	↔	↔	↔	No dose adjustment of oral contraceptives is required.
	Norgestrel	↔	↑ 1.2 (0.98, 1.5)	↑ 1.2 (1.0, 1.5)	
	Ethinyl estradiol	↔	↔	↔	
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ velpatasvir (100 mg once daily)[d]	Norelgestromin	↔	↔	↔	No dose adjustment of oral contraceptives is required.
	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%.

4.6 Use in special populations

Pregnancy

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

Sofosbuvir

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

Velpatasvir

Animal studies have shown a possible link to reproductive toxicity.
As a precautionary measure, Sofosbuvir/velpatasvir use is not recommended during pregnancy.

Breast-feeding

It is unknown whether 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 should not be used during breast-feeding.

Fertility

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

Paediatric Use

The pharmacokinetics, safety, and effectiveness of Sofosbuvir + Velpatasvir for treatment of HCV genotype 1, 2, 3, 4, or 6 infection in treatment-naïve and treatment-experienced pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis have been established in an open-label, multicenter clinical trial (Study 1143, N=216; 190 treatment-naïve, 26 treatment-experienced). No clinically meaningful differences in pharmacokinetics were observed in comparison to those observed in adults.
The safety and effectiveness in pediatric subjects were comparable to those observed in adults. However, among the 41 pediatric subjects less than 6 years of age, vomiting and product use issue (spitting up the drug) were reported more frequently (15% and 10%, respectively; all Grade 1 or 2) compared to subjects 6 years of age and older. Five subjects (12%) discontinued treatment after vomiting or spitting up the drug.
The safety and effectiveness of Sofosbuvir + Velpatasvir for treatment of HCV genotype 5 in pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis are supported by sofosbuvir, GS-331007, and velpatasvir exposures in adults and pediatric patients. Similar rationale is used to support dosing recommendations for pediatric patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection who have decompensated cirrhosis (Child-Pugh B or C).

Geriatric Use

Clinical trials of Sofosbuvir/velpatasvir included 156 subjects aged 65 and over (12% of total number of subjects in the Phase 3 clinical trials). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of sofosbuvir and velpatasvir is warranted in geriatric patients.

Hepatic Impairment

No dosage adjustment of sofosbuvir and velpatasvir is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).
Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with Sofosbuvir/velpatasvir and ribavirin.

Renal Impairment

No dosage adjustment of sofosbuvir and velpatasvir is required for patients with mild or moderate renal impairment including ESRD requiring dialysis. No safety data are available in subjects with both decompensated cirrhosis and severe renal impairment, including ESRD requiring dialysis. Additionally, no safety data are available in pediatric patients with renal impairment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

The following serious adverse reactions are described below and elsewhere in labelling. Serious symptomatic bradycardia when Sofosbuvir is co-administered with amiodarone and another HCV direct acting antiviral.

Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. If Sofosbuvir/Velpatasvir is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions.

Clinical Trials in Adult Subjects

Adverse reactions in subjects without cirrhosis or with compensated cirrhosis

The adverse reactions data for sofosbuvir and velpatasvir in patients without cirrhosis or with compensated cirrhosis were derived from three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which evaluated a total of 1035 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV, without cirrhosis or with compensated cirrhosis, who received sofosbuvir and velpatasvir for 12 weeks. Sofosbuvir and velpatasvir was studied in placebo- and active controlled trials.
The proportion of subjects who permanently discontinued treatment due to adverse events was 0.2% for subjects who received sofosbuvir and velpatasvir for 12 weeks.
The most common adverse reactions (adverse events assessed as causally related by the investigator and at least 10%) were headache and fatigue in subjects treated with sofosbuvir and velpatasvir for 12 weeks.
Adverse reactions, all grades, observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with sofosbuvir and velpatasvir in ASTRAL-1 include headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Of subjects receiving sofosbuvir and velpatasvir who experienced these adverse reactions, 79% had an adverse reaction of mild severity (Grade 1). With the exception of asthenia, each of these adverse reactions occurred at a similar frequency or more frequently in subjects treated with placebo compared to subjects treated with sofosbuvir and velpatasvir (asthenia: 3% versus 5% for the placebo and sofosbuvir/velpatasvir groups, respectively).
The adverse reactions observed in subjects treated with sofosbuvir and velpatasvir in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Irritability was also observed in greater than or equal to 5% of subjects treated with sofosbuvir and velpatasvir in ASTRAL-3.

Adverse Reactions in Subjects Coinfected with HCV and HIV-1

The safety assessment of Sofosbuvir/velpatasvir in subjects with HCV/HIV-1 coinfection was based on an open-label clinical trial (ASTRAL-5) in 106 subjects who were on stable antiretroviral therapy. The safety profile in HCV/HIV-1 coinfected subjects was similar to that observed in HCV mono-infected subjects. The most common adverse reactions occurring in at least 10% of subjects were fatigue (22%) and headache (10%).

Adverse reactions in subjects with decompensated cirrhosis

The safety assessment of sofosbuvir and velpatasvir in subjects infected with genotype 1, 2, 3, 4 or 6 HCV with decompensated cirrhosis was based on one Phase 3 trial (ASTRAL-4) including 87 subjects who received sofosbuvir and velpatasvir with ribavirin for 12 weeks. All 87 subjects had Child-Pugh B cirrhosis at screening. On the first day of treatment with sofosbuvir and velpatasvir with ribavirin, 6 subjects and 4 subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively.
The most common adverse reactions (adverse events assessed as causally related by the investigator, all grades with frequency of 10% or greater) in the 87 subjects who received sofosbuvir and velpatasvir with ribavirin for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%). Of subjects who experienced these adverse reactions, 98% had adverse reactions of mild to moderate in severity.
A total of 4 (5%) subjects permanently discontinued sofosbuvir and velpatasvir with ribavirin due to an adverse event; there was no adverse event leading to discontinuation that occurred in more than 1 subject.
Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 23% and 7% of subjects treated with sofosbuvir and velpatasvir with ribavirin for 12 weeks, respectively. Ribavirin was permanently discontinued in 17% of subjects treated with sofosbuvir and velpatasvir with ribavirin for 12 weeks, due to adverse reactions.

Less Common Adverse Reactions Reported in Clinical Trials

The following adverse reactions occurred in less than 5% of subjects without cirrhosis or with compensated cirrhosis treated with sofosbuvir and velpatasvir for 12 weeks and are included because of a potential causal relationship.
Rash: In the ASTRAL-1 study, rash occurred in 2% of subjects treated with sofosbuvir/velpatasvir and in 1% of subjects treated with placebo. No serious adverse reactions of rash occurred and all rashes were mild or moderate in severity.
Depression: In the ASTRAL-1 study, depressed mood occurred in 1% of subjects treated with sofosbuvir/velpatasvir and was not reported by any subject taking placebo. No serious adverse reactions of depressed mood occurred and all events were mild or moderate in severity.
The following adverse reactions occurred in less than 10% of subjects with decompensated cirrhosis (ASTRAL-4) treated with sofosbuvir and velpatasvir with ribavirin for 12 weeks and are included because of a potential causal relationship.
Rash: Rash occurred in 5% of subjects treated with sofosbuvir and velpatasvir with ribavirin. No serious adverse reactions of rash occurred and all rashes were mild or moderate in severity.

Laboratory abnormalities

Lipase elevations: In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 3% and 1% of subjects treated with sofosbuvir and velpatasvir and placebo for 12 weeks, respectively; and in 6% and 3% of subjects treated with sofosbuvir and velpatasvir in ASTRAL-2 and ASTRAL-3, respectively.
In the Phase 3 trial of subjects with decompensated cirrhosis (ASTRAL-4), lipase was assessed when amylase values were greater than or equal to 1.5xULN. Isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 2% of subjects treated with sofosbuvir/velpatasvir with ribavirin for 12 weeks.
Creatine Kinase: In ASTRAL-1, isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% and 0% of subjects treated with sofosbuvir/velpatasvir and placebo for 12 weeks, respectively; and in 2% and 1% of subjects treated with sofosbuvir/velpatasvir in ASTRAL-2 and ASTRAL-3, respectively.
In the Phase 3 trial with decompensated cirrhosis (ASTRAL-4), isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of subjects treated with sofosbuvir/velpatasvir with ribavirin for 12 weeks.
Indirect Bilirubin: Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-1/HCV coinfected subjects treated with sofosbuvir/velpatasvir and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of sofosbuvir/velpatasvir without dose adjustment or treatment interruption of either sofosbuvir/velpatasvir or HIV antiretroviral agents.

Adverse Reactions in Adult Liver Transplant Recipients

The safety assessment of Sofosbuvir + Velpatasvir in liver transplant recipients was based on an open-label clinical trial (Trial 2104) in 79 adults without cirrhosis or with compensated cirrhosis who received Sofosbuvir + Velpatasvir for 12 weeks. One subject discontinued treatment due to an adverse event on Day 7. The adverse reactions observed were consistent with the known safety profile of Sofosbuvir + Velpatasvir. Adverse reactions occurring in at least 5% of subjects were headache (18%), fatigue (15%), nausea (8%), diarrhea (6%), and asthenia (5%).

Adverse Reactions in Adults with Severe Renal Impairment Requiring Dialysis

In an open-label trial (Trial 4062), in which a total of 59 adults with HCV with compensated liver disease (with or without cirrhosis) and ESRD requiring dialysis received Sofosbuvir/velpatasvir for 12 weeks, the most common adverse reaction was nausea (7%).

Adverse Reactions in Pediatric Subjects 3 Years of Age and Older

The safety assessment of Sofosbuvir + Velpatasvir in pediatric subjects 3 years of age and older is based on data from a Phase 2, open-label clinical trial (Study 1143) that enrolled 216 subjects who were treated with Sofosbuvir + Velpatasvir for 12 weeks. The adverse reactions observed in pediatric subjects 6 years of age and older were consistent with those observed in clinical trials of Sofosbuvir + Velpatasvir in adults.
Among the 41 pediatric subjects less than 6 years of age, gastrointestinal adverse reactions were reported more commonly compared to subjects 6 years of age and older. Vomiting and product use issue (spitting up the drug) were reported in 15% and 10% of subjects, respectively; these adverse reactions were mild (Grade 1 or 2) and led to treatment discontinuation in 5 (12%) subjects.

Post-marketing experience

The following adverse reactions have been identified during post approval use of sofosbuvir. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders: Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with sofosbuvir in combination with another HCV direct acting antiviral.

Skin and Subcutaneous Tissue Disorders: Skin rashes, sometimes with blisters or angioedema-like swelling, angioedema.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form **(form.heteroworld.com)** or by **Hetero Helpline No. 1800-120-8689.** Also for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.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, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.
No specific antidote is available for overdose with sofosbuvir and velpatasvir. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with sofosbuvir and 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, 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 Mechanism of action

Sofosbuvir

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

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.

5.2 Pharmacodynamic properties

Cardiac Electrophysiology

The effect of sofosbuvir 400 mg (recommended dosage) and 1200 mg (3 times the recommended dosage) on QTc interval was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT trial. At a dose 3 times the recommended dose, sofosbuvir does not prolong QTc to any clinically relevant extent.
The effect of velpatasvir 500 mg (5 times the recommended dosage) was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT trial. At a dose 5 times the recommended dose, velpatasvir does not prolong QTc interval to any clinically relevant extent.

5.3 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.
Based on the population pharmacokinetic analysis in HCV-infected patients, mean steady-state $AUC_{0\text{-}24}$ for sofosbuvir (n = 982), GS-331007 (n = 1,428) and velpatasvir (n = 1,425) were 1,260, 13,970 and 2,970 ng•h/mL, respectively. Steady-state C_{max} for sofosbuvir, GS-331007 and velpatasvir were 566, 868 and 259 ng/mL, respectively. Sofosbuvir and GS-331007 AUC0-24 and C_{max} were similar in healthy adult subjects and patients with HCV infection. Relative to healthy subjects (n = 331), velpatasvir $AUC_{0\text{-}24}$ and C_{max} were 37% lower and 41% lower, respectively in HCV-infected patients.

Effects of food

Relative to fasting conditions, the administration of a single dose of sofosbuvir and velpatasvir with a moderate fat (~600 kcal, 30% fat) or high fat (~800 kcal, 50% fat) meal resulted in a 34% and 21% increase in velpatasvir $AUC_{0-\infty}$, respectively, and a 31% and 5% increase in velpatasvir C_{max}, respectively. The moderate or high fat meal increased sofosbuvir AUC0-∞ by 60% and 78%, respectively, but did not substantially affect the sofosbuvir C_{max}. The moderate or high fat meal did not alter GS-331007 $AUC_{0-\infty}$, but resulted in a 25% and 37% decrease in its C_{max}, respectively. The response rates in Phase 3 studies were similar in HCV-infected patients who received sofosbuvir and velpatasvir with food or without food. Sofosbuvir and velpatasvir can be administered without regard to food.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity was approximately 0.7.
Velpatasvir is > 99.5% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09 µg/mL to 1.8 µg/mL. After a single 100 mg dose of [^{14}C]-velpatasvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.52 and 0.67.

Metabolism

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately > 90% of total systemic exposure.
Velpatasvir is a substrate of CYP2B6, CYP2C8, and CYP3A4 with slow turnover. Following a single dose of 100 mg [^{14}C]-velpatasvir, the majority (> 98%) of radioactivity in plasma was parent drug. The monohydroxylated and desmethylated velpatasvir were the metabolites identified in human plasma. Unchanged velpatasvir is the major species present in faeces.

Excretion

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the [^{14}C]-radioactivity was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of Sofosbuvir/Velpatasvir were 0.5 and 25 hours, respectively.
Following a single 100 mg oral dose of [^{14}C]-velpatasvir, mean total recovery of the [^{14}C]-radioactivity was 95%, consisting of approximately 94% and 0.4% recovered from the faeces and urine, respectively. Unchanged velpatasvir was the major species in faeces accounting for a mean of 77% of the administered dose, followed by monohydroxylated velpatasvir (5.9%) and desmethylated velpatasvir (3.0%). These data indicate that biliary excretion of parent drug was a major route of elimination for velpatasvir. The median terminal half-life of velpatasvir following administration of sofosbuvir and velpatasvir was approximately 15 hours.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

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.

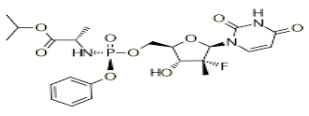
Velpatasvir

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.

7. DESCRIPTION

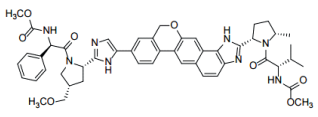
Sofosbuvir

Sofosbuvir is a nucleotide analog hepatitis C virus non-structural protein 5B (HCV NS5B) polymerase inhibitor. The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5 (2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy) (phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



Velpatasvir

Velpatasvir is a HCV NS5A inhibitor. The IUPAC name for velpatasvir is Methyl {(1R)-2-[(2S,4S)-2-(5-{2[(2S,5S)-1-((2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl)-5-methylpyrrolidin-2-yl]1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4 (methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of C49H54 N8O8 and a molecular weight of 883.0. It has the following structural formula:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Shelf-life

Refer on pack

8.3 Packing Information

Each bottle contains 28 tablets, polyester coil, and is closed with a child-resistant closure.

8.4 Storage and handling instructions

- **Store protected from moisture at a temperature not exceeding 30°C.**
- Keep container tightly closed. Keep out of reach of children.
- Dispense in original container.
- Do not use if seal over bottle opening is broken or missing.

9. PATIENT COUNSELLING INFORMATION

Risk of Hepatitis B Virus Reactivation in Patients Confected with HCV and HBV

Inform patients that HBV reactivation can occur in patients coinfected with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of HBV infection.

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Advise patients to seek medical evaluation immediately for symptoms of bradycardia such as near-fainting or fainting, dizziness or light-headedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems

Drug Interactions

Inform patients that Sofosbuvir and velpatasvir may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort.

Administration

Advise patients to take Sofosbuvir and velpatasvir once daily on a regular dosing schedule with or without food. Inform patients that it is important not to miss or skip doses and to take Sofosbuvir and velpatasvir for the duration that is recommended by the physician.

Pregnancy

Advise patients to avoid pregnancy during combination treatment with Sofosbuvir, velpatasvir and ribavirin and for 6 months after completion of treatment. Inform patients to notify their healthcare provider immediately in the event of a pregnancy.

10. DETAILS OF MANUFACTURER

Hetero Labs Limited (Unit-II)
Village: Kalyanpur, Chakkan Road,
Tehsil: Baddi, Distt.: Solan,
Himachal Pradesh - 173 205.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

MF-ND/85/2017, 04th May 2017.

12. DATE OF REVISION

17-08-2024

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Plot # 9D, Delhi - 110032

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Back

Colour: Black
Spec.: 41± 15% Gsm Bible Paper
Dimension: 160x520 mm
Fold Size: 40x65 mm
Reason for change: Artwork revised as per IP addendum 2024