Velscot Tablets*

ویل سکاٹ ٹیبلٹس

WARNING

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

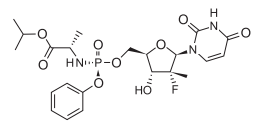
Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with VELSCOT. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV 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 management for HBV infection as clinically indicated.

COMPOSITION: Each film coated tablet contains:

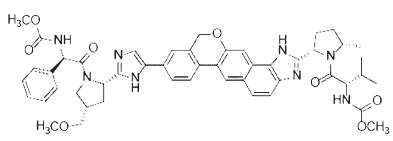
Sofosbuvir* …..... 400 mg & Velpatasvir*…..... 100 mg.

DESCRIPTION: VELSCOT is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor and velpatasvir is an NS5A inhibitor.

Sofosbuvir: 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-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2-7.7 at 37 °C and is slightly soluble in water. It has the following structural formula:



Velpatasvir: 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 $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0. Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2. It has the following structural formula:



CLINICAL PHARMACOLOGY: Mechanism of Action: VELSCOT is a fixed-dose combination of sofosbuvir and velpatasvir which are direct-acting antiviral agents against the hepatitis C virus. **Sofosbuvir:** Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 inhibits the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC 50 value ranging from 0.36 to 3.3 micromolar. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase. **Velpatasvir:** Velpatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action. **Pharmacodynamics:** ***Cardiac Electrophysiology:*** Sofosbuvir does not prolong QTc to any clinically relevant extent. At a dose 5 times the recommended dose, velpatasvir does not prolong QTc interval to any clinically relevant extent. **Pharmacokinetics:** The pharmacokinetic properties of the components of VELSCOT are provided in Table 1.

Table 1: Pharmacokinetic Properties of the Components of VELSCOT.

	Sofosbuvir	Velpatasvir
Absorption		
Tmax (h)	0.5-1	3
Effect of moderate meal (relative to fasting)[a]	↑ 60%	↑ 34%
Effect of high fat meal (relative to fasting)[a]	↑ 78%	↑ 21%
Distribution		
% Bound to human plasma proteins	61-65	>99.5
Blood-to-plasma ratio	0.7	0.52.67
Metabolism		
Metabolism	Cathepsin A CES1 HINT1	CYP2B6 CYP2C8 CYP3A4
Elimination		
Major route of elimination	Sofosbuvir: Metabolism, GS-331007[b]: Glomerular filtration and active tubular secretion	Biliary excretion as parent (77%)
$t_{1/2}$ (h)[c]	Sofosbuvir: 0.5 GS-331007[b]: 25	15
% of dose excreted in urine[d]	80[e]	0.4
% of dose excreted in feces[d]	14	94

CES1 = carboxylesterase 1; HINT1 = histidine triad nucleotide-binding protein 1.

a. Values refer to mean systemic exposure. Moderate meal = ~600 kcal, 30% fat; high fat meal = ~800 kcal, 50% fat. VELSCOT can be taken with or without food.

B .GS -331007 is the primary circulating nucleoside metabolite of sofosbuvir.

c. $t_{1/2}$ values refer to median terminal plasma half-life.

d. Single dose administration.

e. Predominantly as GS-331007.

INDICATIONS AND USAGE: VELSCOT is indicated for the treatment of adult patients with chronic hepatitis C virus (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.

CONTRAINDICATIONS: VELSCOT and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated.

ADVERSE REACTIONS: The serious adverse reactions is serious symptomatic bradycardia when coadministered with amiodarone. If VELSCOT is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions. The most common adverse reactions are headache, fatigue, nausea , asthenia, and insomnia and are of mild severity. The most common adverse reactions with ribavirin are fatigue, anemia , nausea, headache, insomnia, and diarrhea.

Laboratory Abnormalities: • Lipase elevations • Creatine kinase elevations • Increases in indirect bilirubin

DRUG INTERACTIONS: Potential for Other Drugs to Affect VELSCOT: Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. Slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 is 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 VELSCOT. The use of these agents with VELSCOT is not recommended. VELSCOT may be coadministered with P-gp, BCRP, and CYP inhibitors. **Potential for VELSCOT to Affect Other Drugs:** Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. Coadministration of VELSCOT with drugs that are substrates of these transporters may increase the exposure of such drugs. **Established and Potentially Significant Drug Interactions:** Table 2 provides a listing of established or potentially clinically significant drug interactions.

Table 2: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Acid Reducing Agents:	↓ Velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		Separate antacid and VELSCOT administration by 4 hours.
H_2-receptor antagonists (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from VELSCOT at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors (e.g., omeprazole)		Coadministration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to coadminister, VELSCOT should be administered with food and taken 4 hours before omeprazole 20 mg.
Antiarrhythmics: Amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Coadministration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with VELSCOT is not recommended; if coadministration is required, cardiac monitoring is recommended.
Digoxin	↑ Digoxin	Therapeutic concentration monitoring of digoxin is recommended when coadministered with VELSCOT. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: Topotecan	↑ Topotecan	Coadministration is not recommended.
Anticonvulsants: Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	↓ Sofosbuvir ↓ Velpatasvir	Coadministration is not recommended.
Antimycobacterials: Rifabutin Rifampin Rifapentine	↓ Sofosbuvir ↓ Velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals: Efavirenz	↓ Velpatasvir	Coadministration of VELSCOT with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↑ Tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving VELSCOT concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
Tipranavir/Ritonavir	↓ Sofosbuvir ↓ Velpatasvir	Coadministration is not recommended.
Herbal Supplements: St. John's wort (*Hypericum perforatum*)	↓ Sofosbuvir ↓ Velpatasvir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: Rosuvastatin	↑ Rosuvastatin	Coadministration of VELSCOT with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy,including rhabdomyolysis. Rosuvastatin may be administered with VELSCOT at a dose that does not exceed 10 mg.
Atorvastatin	↑ Atorvastatin	Coadministration of VELSCOT with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopath, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

DF = Disoproxil fumarate. a. This table is not all inclusive. b. ↓ = decrease, ↑ = increase.

USE IN SPECIFIC POPULATION: Pregnancy: If VELSCOT is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on ribavirin-associated risks of use during pregnancy. The background risk of major birth defects and miscarriage for the indicated population is unknown. **Lactation:** It is not known whether the components of VELSCOT and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for VELSCOT and any potential adverse effects on the breastfed child from VELSCOT or from the underlying maternal condition. If VELSCOT is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use during lactation. **Females and Males of Reproductive Potential:** If VELSCOT is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. **Pediatric Use:** Safety and effectiveness have not been established in pediatric patients. **Geriatric Use:** No dosage adjustment is warranted in geriatric patients. **Renal Impairment:** No dosage adjustment is required for patients with mild or moderate renal impairment. The safety and efficacy have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD requiring hemodialysis. **Hepatic Impairment:** No dosage adjustment 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 VELSCOTand ribavirin.

WARNINGS AND PRECAUTIONS: Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV: Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients. HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increases in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur. Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with VELSCOT. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with VELSCOT and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. **Serious Symptomatic Bradycardia When Coadministered with Amiodarone:** Cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir containing regimen. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this bradycardia effect is unknown. Coadministration of amiodarone with VELSCOT is not recommended. For patients taking amiodarone who have no alternative treatment options and who will be coadministered VELSCOT:

- Counsel patients about the risk of serious symptomatic bradycardia.
- Cardiac monitoring in an inpatient setting for the first 48 hours of coadministration is recommended, 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.

Patients who are taking VELSCOT who need to start amiodarone therapy due to no other alternative treatment options should undergo similar cardiac monitoring as outlined above. Due to amiodarone's long elimination half-life, patients discontinuing amiodarone just prior to starting sofosbuvir in combination with daclatasvir should also undergo similar cardiac monitoring as outlined above. **Risk of Reduced Therapeutic Effect Due to Concomitant Use of VELSCOT with Inducers of P-gp and/or Moderate to Potent Inducers of CYP:** Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to potentially reduced therapeutic effect of VELSCOT. The use of these agents with VELSCOT is not recommended. **Risks Associated with Ribavirin and VELSCOT Combination Treatment:** If VELSCOT is administered with ribavirin, the warnings and precautions for ribavirin apply to this combination regimen.

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 VELSCOT. **Recommended Dosage:** The recommended dosage of VELSCOT Tablet 400/100 mg is one tablet taken orally once daily with or without food. Table 3 shows the recommended treatment regimen and duration based on patient population.

Table 3: Recommended Treatment Regimen in Patients with Genotype 1, 2, 3, 4, 5, or 6 HCV

Patient Population	Treatment Regimen & Duration
Treatment-naïve and treatment-experienced[a], without cirrhosis and with compensated cirrhosis (Child-Pugh A)	VELSCOT 12 Weeks
Treatment-naïve and treatment-experienced[a], with decompensated cirrhosis (Child-Pugh B or C)	VELSCOT + Ribavirin[a] 12 Weeks

a. Regimens containing peginterferon alfa/ribavirin with or without an HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir).

b. When administered with VELSCOT, the recommended dosage of ribavirin is based on weight (administered with food): 1000 mg per day for patients less than 75 kg and 1200 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.

No Dosage Recommendations in Severe Renal Impairment and End Stage Renal Disease: No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73 m^2) or with end stage renal disease (ESRD), due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

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

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place below 30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION: VELSCOT Tablets are available in packing containing 28 film coated tablets.

*Scotmann Specs.

خوراک: رجسٹرڈ میڈیکل پریکٹشنرز کی ہدایت کے مطابق۔

احتیاط: ٹھنڈی، خشک اور تاریک جگہ پر 30 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔

بچوں کی پہنچ سے دور رکھیں۔

رجسٹرڈ میڈیکل پریکٹشنرز کے نسخہ پر فروخت اور استعمال کریں۔

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