Velpaget™

[Sofosbuvir+Velpatasvir]

Tablets 400mg+100mg

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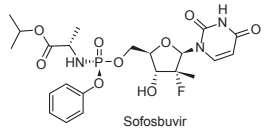
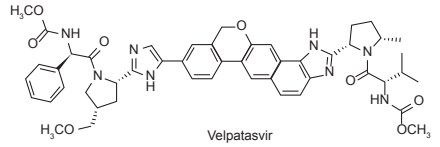
DESCRIPTION
Velpaget (Sofosbuvir + Velpatasvir) is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration.
Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor. Chemically, it is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5 (2,4-dioxo-3,4- dihydropyrimidin-1(2H)-yl) -4-fluoro-3-hydroxy-4-methyltetrahydrofuran -2-yl)methoxy)-(phenoxy) phosphoryl amino) propanoate. Its molecular formula is $C_{22}H_{29}FN_3O_9P$ and the structural formula is:



Sofosbuvir

Velpatasvir is an NS5A inhibitor. Chemically, it 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-phenyl ethyl}carbamate. Its molecular formula is $C_{49}H_{54}N_8O_8$ and the structural formula is:



Velpatasvir

QUALITATIVE & QUANTITATIVE COMPOSITION
Velpaget (Sofosbuvir + Velpatasvir) is available for oral administration as:

Velpaget Tablets 400mg + 100mg
Each film-coated tablet contains:
Sofosbuvir... 400mg
Velpatasvir... 100mg

CLINICAL PHARMACOLOGY
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 analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator.

Velpatasvir:
Velpatasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

Pharmacokinetics
Absorption
Sofosbuvir:
Following oral administration, 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:
Velpatasvir median peak concentrations were observed at 3 hours post-dose.

Effect 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}. The moderate or high fat meal did not alter GS-331007 $AUC_{0\text{-}inf}$, but resulted in a 25% and 37% decrease in its C_{max} respectively. Sofosbuvir + Velpatasvir can be administered without regard to food.

Distribution
Sofosbuvir:
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:
Velpatasvir is >99.5% bound to human plasma proteins and binding is independent of drug concentration over the range of 0.09µg/mL to 1.8µg/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.

Metabolism
Sofosbuvir:
Sofosbuvir is extensively metabolized 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 catalyzed 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 400mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately > 90% of total systemic exposure.

Velpatasvir:
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 feces.

Excretion
Sofosbuvir:
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, feces and expired air respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration were 0.5 and 25 hours, respectively.

Velpatasvir:
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%). This 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 was approximately 15 hours.

Special Population
Patients with Renal impairment
Relative to patients with normal renal function (eGFR > 80mL/min/1.73 m²), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In patients with ESRD, sofosbuvir $AUC_{0\text{-}inf}$ was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis, respectively. The $AUC_{0\text{-}inf}$ of GS-331007 in patients with ESRD administered with sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively. GS-331007 is efficiently removed by hemodialysis with an extraction coefficient of approximately 53%.

The pharmacokinetics of velpatasvir was studied in HCV negative patients with severe renal impairment. Relative to subjects with normal renal function, velpatasvir AUC_{inf} was 50% higher in subjects with severe renal impairment.

Patients with Hepatic impairment
The pharmacokinetics of sofosbuvir was studied in HCV-infected patients with moderate and severe hepatic impairment. 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.

The pharmacokinetics of velpatasvir was studied in HCV negative patients with moderate and severe hepatic impairment. Compared to subjects with normal hepatic function velpatasvir total plasma exposure (AUC_{inf}) was similar in patients with moderate or severe hepatic impairment.

THERAPEUTIC INDICATIONS
Velpaget (Sofosbuvir + Velpatasvir) is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6:
- Without cirrhosis or with compensated cirrhosis.
- With decompensated cirrhosis for use in combination with ribavirin.

DOSAGE AND ADMINISTRATION
The recommended dosage of Velpaget (Sofosbuvir + Velpatasvir) is one tablet taken orally once daily with or without food.

Recommended Treatment and Duration for all HCV Genotypes

Patient Population	Treatment Regimen and Duration
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	Velpaget (Sofosbuvir + Velpatasvir) 12 weeks Addition of ribavirin[a] may be considered for genotype 3 infected patients with compensated cirrhosis.
Patients with decompensated cirrhosis (Child-Pugh B and C)	Velpaget (Sofosbuvir + Velpatasvir) + ribavirin[a] 12 weeks

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

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

If a dose of Velpaget (Sofosbuvir + Velpatasvir) is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose of Velpaget (Sofosbuvir + Velpatasvir) at the usual time. Patients should be instructed not to take a double dose of Velpaget (Sofosbuvir + Velpatasvir).

Patients who have previously failed therapy with an NS5A-containing regimen:
Velpaget (Sofosbuvir + Velpatasvir) + ribavirin for 24 weeks may be considered.

Special Population
Renal impairment
No dose adjustment of Velpaget (Sofosbuvir + Velpatasvir) is required for patients with mild or moderate renal impairment. The safety and efficacy of Velpaget (Sofosbuvir + Velpatasvir) has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) or End Stage Renal Disease (ESRD) requiring hemodialysis.

Hepatic impairment
No dose adjustment of Velpaget (Sofosbuvir + Velpatasvir) is required for patients with mild, moderate or severe hepatic impairment.

Elderly
No dose adjustment is warranted for elderly patients.

Pediatric population
The safety and efficacy of Velpaget (Sofosbuvir + Velpatasvir) in children and adolescents aged less than 18 years have not yet been established.

ADVERSE REACTIONS
The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with sofosbuvir + velpatasvir for 12 weeks are headache, fatigue, nausea, nasopharyngitis, insomnia, diarrhea, asthenia, cough, back pain and arthralgia.

The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with sofosbuvir + velpatasvir and ribavirin for 12 weeks in patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia and diarrhea.

CONTRAINDICATIONS
- Sofosbuvir + velpatasvir is contraindicated in patients with known hypersensitivity to sofosbuvir or to velpatasvir or to any excipient of the product.
- Sofosbuvir + velpatasvir and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated.
- Sofosbuvir + velpatasvir should not be administered concurrently with other medicinal products containing any of the same active components.

PRECAUTIONS

WARNINGS: RISK OF HEPATITIS B VIRUS (HBV) REACTIVATION
Direct acting anti-viral have been associated with hepatitis B virus (HBV) reactivation in patients who have a current or previous infection with HBV and are treated with certain Direct-Acting Antiviral (DAA) medicines for hepatitis C virus.
Health Care Professionals should screen all patients for evidence of current or prior HBV infection before starting treatment with DAAs and monitor patients through blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up.

- Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV co-infected 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. 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.
  Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with sofosbuvir + velpatasvir. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with sofosbuvir + velpatasvir and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.
- Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Co-administration of amiodarone with sofosbuvir + velpatasvir is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended.
- If sofosbuvir + velpatasvir is administered with ribavirin, the warnings and precautions for ribavirin apply to this combination regimen.

Pregnancy
There are no adequate and well controlled studies with sofosbuvir + velpatasvir in pregnant women. Sofosbuvir + velpatasvir is not recommended during pregnancy.

Nursing Mother
It is not known whether sofosbuvir, metabolites of sofosbuvir or velpatasvir are excreted in human milk. A risk to newborn / infants cannot be excluded. Therefore, sofosbuvir + velpatasvir should not be used during breast-feeding.

DRUG INTERACTIONS
- 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 significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to potentially reduced therapeutic effect of sofosbuvir + velpatasvir. The use of these agents with sofosbuvir + velpatasvir is not recommended.
- Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3 and OATP2B1. Co-administration of sofosbuvir + velpatasvir with drugs that are substrates of these transporters may increase the exposure of such drugs.

Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Effect / Recommendation
Acid Reducing Agents:		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)	↓ velpatasvir	Separate antacid and sofosbuvir + velpatasvir administration by 4 hours.
H_2 - receptor antagonists[a] (e.g., famotidine)		H_2 - receptor antagonists may be administered simultaneously with or 12 hours apart from sofosbuvir + velpatasvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily.
Proton-pump inhibitors[a] (e.g., omeprazole)		Co-administration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to co-administer, sofosbuvir + velpatasvir should be administered with food and taken 4 hours before omeprazole 20mg.
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir and velpatasvir concentrations unknown	Co-administration of amiodarone with sofosbuvir + velpatasvir may result in serious symptomatic bradycardia. Co-administration of amiodarone with sofosbuvir + velpatasvir is not recommended; if co-administration is required, cardiac monitoring is recommended.
Digoxin[a]	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when co-administered with sofosbuvir + velpatasvir.
Anticancers: topotecan	↑ topotecan	Co-administration is not recommended.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
Antimycobacterials: rifabutin rifampin[a] rifapentine	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
HIV Antiretrovirals: Efavirenz[a]	↓ velpatasvir	Co-administration of sofosbuvir + velpatasvir with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir disoproxil fumarate	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving sofosbuvir + velpatasvir concomitantly with a regimen containing tenofovir disoproxil fumarate.
Tipranavir / ritonavir	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ sofosbuvir ↓ velpatasvir	Co-administration is not recommended.
HMG-CoA Reductase Inhibitors: rosuvastatin[a]	↑ rosuvastatin	Co-administration of sofosbuvir + velpatasvir with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with sofosbuvir + velpatasvir at a dose that does not exceed 10mg.
atorvastatin	↑ atorvastatin	Co-administration of sofosbuvir + velpatasvir with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

a. Interactions studied in healthy adults

OVERDOSAGE
No specific antidote is available for overdosage. 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. 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
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Velpaget (Sofosbuvir + Velpatasvir) Tablets 400mg + 100mg are available in a pack of 28's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
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