

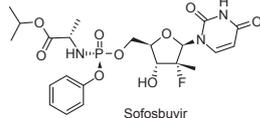
Velfos™

[Sofosbuvir+Velpatasvir Tablets]

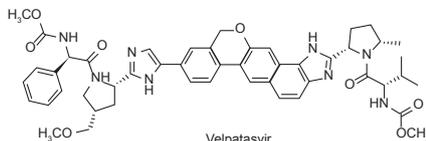
400mg+100mg

DESCRIPTION

Velfos (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) phosphonyl amino) propanoate. Its molecular formula is $C_{22}H_{29}FN_3O_8P$ and the structural formula is:



Velpatasvir is an NS5A inhibitor. Chemically, it is methyl {(1R)-2-((2S,4S)-2-(5-((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. Its molecular formula is $C_{49}H_{54}N_6O_8$ and the structural formula is:



QUALITATIVE & QUANTITATIVE COMPOSITION

Velfos (Sofosbuvir + Velpatasvir) is available for oral administration as:

Velfos 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_{0-24} , respectively, and a 31% and 5% increase in velpatasvir C_{max} , respectively. The moderate or high fat meal increased sofosbuvir AUC_{0-24} 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_{0-24} , 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 μ g/mL to 20 μ g/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:

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

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 biosynthesis 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:

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 feces.

Excretion

Sofosbuvir:

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, 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 indicates 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 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 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_{0-24} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{0-24} was 55%, 88% and 451% higher, respectively. In patients with ESRD, sofosbuvir AUC_{0-24} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis, respectively. The AUC_{0-24} 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_{0-24} 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_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} 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_{0-24}) was similar in patients with moderate or severe hepatic impairment.

THERAPEUTIC INDICATIONS

Velfos (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 Velfos (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) | Velfos (Sofosbuvir + Velpatasvir) 12 weeks Addition of ribavirin* may be considered for genotype 3 infected patients with compensated cirrhosis. |
| Patients with decompensated cirrhosis (Child-Pugh B and C) | Velfos (Sofosbuvir + Velpatasvir) + ribavirin* 12 weeks |

a. When administered with Velfos (Sofosbuvir + Velpatasvir), 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.

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

If a dose of Velfos (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 Velfos (Sofosbuvir + Velpatasvir) at the usual time. Patients should be instructed not to take a double dose of Velfos (Sofosbuvir + Velpatasvir).

Patients who have previously failed therapy with an NS5A-containing regimen:

Velfos (Sofosbuvir + Velpatasvir) + ribavirin for 24 weeks may be considered.

Special Population

Renal impairment

No dose adjustment of Velfos (Sofosbuvir + Velpatasvir) is required for patients with mild or moderate renal impairment. The safety and efficacy of Velfos (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 Velfos (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 Velfos (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

- 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, metabolite 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) | | Separate antacid and sofosbuvir + velpatasvir administration by 4 hours. |
| H ₂ - receptor antagonists* (e.g., famotidine) | ↓ velpatasvir | 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* (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* | ↑ 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* rifapentine | ↓ sofosbuvir ↓ velpatasvir | Co-administration is not recommended. |
| HIV Antiretrovirals: Efavirenz* | ↓ 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* | ↑ rosuvastatin | Coadministration 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 overdose. 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

Velfos (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.



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