Sofosvel

Sofosbuvir + Velpatasvir

COMPOSITION

Sofosvel Tablet: Each film coated tablet contains Sofosbuvir INN 400 mg and Velpatasvir INN 100 mg.

PHARMACOLOGICAL INFORMATION

Therapeutic class: Antiviral agent.

PHARMACOLOGICAL ACTION

Mechanism of Action

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. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with an IC50 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 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

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

The effect of Velpatasvir 500 mg (five times the recommended dosage) was evaluated in an active-controlled (Moxifloxacin 400 mg) thorough QT trial. At a dose five times the recommended dose, Velpatasvir does not prolong QTc interval to any clinically relevant extent.

Pharmacokinetics

The pharmacokinetic properties of the components of Sofosbuvir/Velpatasvir are provided in Table 1.

Table 1: Pharmacokinetic properties of the Components of Sofosbuvir/Velpatasvir

	Sofosbuvir	Velpatasvir
Absorption		
T_{max} (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	0.52-0.67
Metabolism		
Metabolism	Cathepsin A	CYP2B6
	CES1	CYP2C8
	HINT1	CYP3A4
Elimination		
Major route of elimination	SOF: metabolism	Biliary excretion as parent
	GS-331007[b]: glomerular	(77%)
	filtration and active tubular secretion	
$t_{1/2}$ (h)[c]	SOF: 0.5	15
	GS-331007[b]: 25	
% 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. Sofosbuvir/Velpatasvir can be taken with or without food.
b. GS-331007 is the primary circulating nucleoside metabolite of SOF.
c. $t_{1/2}$ values refer to median terminal plasma half-life.
d. Single dose administration of [^{14}C] SOF or [^{14}C] VEL in mass balance studies.
e. Predominantly as GS-331007.

Specific Populations

Pediatric Patients

The pharmacokinetics of Sofosbuvir or Velpatasvir in pediatric patients has not been established.

Geriatric Patients

Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 82 years) analyzed, age did not have a clinically relevant effect on the exposure to Sofosbuvir, GS-331007 or Velpatasvir.

Patients with Renal Impairment

The pharmacokinetics of Sofosbuvir were studied in HCV negative subjects with mild (eGFR between 50 to less than 80 mL/min/1.73 m^2), moderate (eGFR between 30 to less than 50 mL/min/1.73 m^2), severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), and subjects with ESRD requiring hemodialysis following a single 400 mg dose of Sofosbuvir. Relative to subjects with normal renal function (eGFR greater than 80 mL/min/1.73 m^2), the Sofosbuvir $AUC_{0\text{-}inf}$ was 61%,,107%, and 171% higher in subjects with mild, moderate, and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88%, and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, Sofosbuvir and GS-331007 $AUC_{0\text{-}inf}$ was 28% and 1280% higher when Sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when Sofosbuvir was dosed 1 hour after hemodialysis, respectively. A 4 hour hemodialysis session removed approximately 18% of administered dose.

The pharmacokinetics of Velpatasvir were studied with a single dose of 100 mg Velpatasvir in HCV negative subjects with severe renal impairment (eGFR less than 30 mL/min by Cockcroft-Gault). No clinically relevant differences in Velpatasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.

Patients with Hepatic Impairment

The pharmacokinetics of Sofosbuvir were studied following 7-day dosing of 400 mg Sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C, respectively). Relative to subjects with normal hepatic function, the Sofosbuvir $AUC_{0\text{-}24}$ were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of Sofosbuvir and GS-331007.

The pharmacokinetics of Velpatasvir were studied with a single dose of 100 mg Velpatasvir in HCV negative subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in subjects with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV- infected subjects indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of Velpatasvir.

Race

Population pharmacokinetics analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposure of Sofosbuvir, GS-331007 or Velpatasvir.

Gender

Population pharmacokinetics analysis in HCV-infected subjects indicated that gender had no clinically relevant effect on the exposure of Sofosbuvir, GS-331007 or Velpatasvir.

Drug Interaction Studies

After oral administration of Sofosbuvir/Velpatasvir, Sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction (hydrolysis followed by sequential phosphorylation) to form the pharmacologically active triphosphate. In clinical pharmacology studies, both Sofosbuvir and the primary circulating metabolite GS-331007 (dephosphorylated nucleotide metabolite) were monitored for purposes of pharmacokinetic analyses.

Sofosbuvir and Velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Velpatasvir is also transported by OATP1B1 and OATP1B3. In vitro, slow metabolic turnover of Velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed. 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/ Velpatasvir. Coadministration with drugs that inhibit P-gp and/or BCRP may increase Sofosbuvir and/or Velpatasvir plasma concentrations without increasing GS-331007 plasma concentration. Drugs that inhibit CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of Velpatasvir.

Velpatasvir is an inhibitor of drug transporter P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1, and its involvement in drug interactions with these transporters is primarily limited to the process of absorption. At clinically relevant concentration, Velpatasvir is not an inhibitor of hepatic transporters OATP1A2 or OCT1, renal transporters OCT2, OAT1, OAT3 or MATE1, or CYP or UGT1A1 enzymes.

THERAPEUTIC INDICATIONS

Sofosvel 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.

DOSAGE AND ADMINISTRATION

The recommended dosage of Sofosvel is one tablet taken orally once daily with or without food. Table 2 shows the recommended treatment regimen and duration based on patient population.

Table 2: Recommended treatment regimen in patients with genotype 1, 2, 3, 4, 5 or 6 HCV

Patient Population	Treatment Regimen and Duration
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	Sofosbuvir/Velpatasvir 12 weeks
Patients with decompensated cirrhosis (Child-Pugh B or C)	Sofosbuvir/Velpatasvir + Ribavirin[a] 12 weeks

a. When administered with 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. 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.

ADVERSE REACTIONS

The most common side effects observed with Sofosbuvir and Velpatasvir combination were Fatigue, Nausea, Headache, Anemia, Diarrhea, Insomnia, Pruritus, Muscle spasm, Dyspnea and Cough. There are some rare adverse events including reduced hemoglobin level, reduced lymphocyte count, reduced neutrophil count and reduced platelet count.

Serious Symptomatic Bradycardia developed when Sofosbuvir is coadministered with Amiodarone and another HCV Direct Acting Antiviral.

CONTRAINDICATIONS

Sofosvel and Ribavirin combination regimen is contraindicated in patients for whom Ribavirin is contraindicated. Refer to the Ribavirin prescribing information for a list of contraindications for Ribavirin.

DRUG INTERACTIONS

Potential for Other Drugs to Affect Sofosbuvir/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/Velpatasvir. The use of these agents with Sofosbuvir/Velpatasvir is not recommended. Sofosbuvir/Velpatasvir may be coadministered with P-gp, BCRP, and CYP inhibitors.

Potential for Sofosbuvir/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/Velpatasvir with drugs that are substrates of these transporters may increase the exposure of such drugs.

Established and Potentially Significant Drug Interactions

Table 3 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either Sofosbuvir/Velpatasvir, the components of Sofosbuvir/Velpatasvir as individual agents, or are predicted drug interactions that may occur with Sofosbuvir/Velpatasvir.

Table 3: Potentially Significant Drug Interactions: Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction[a]

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 Sofosbuvir/Velpatasvir 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 Sofosbuvir/Velpatasvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., Omeprazole)		Coadministration of Omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to coadminister, Sofosbuvir/Velpatasvir should be administered with food and taken 4 hours before Omeprazole 20 mg. Use with other proton pump- inhibitors has not been studied.
Antiarrhythmics: Amiodarone	Effect on Amiodarone, Sofosbuvir, and Velpatasvir concentrations unknown	Coadministration of Amiodarone with Sofosbuvir/Velpatasvir may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of Amiodarone with Sofosbuvir/Velpatasvir is not recommended; if coadministration is required, cardiac monitoring is recommended.
Digoxin[c]	↑Digoxin	Therapeutic concentration monitoring of Digoxin is recommended when coadministered with Sofosbuvir/Velpatasvir. 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[c], Rifapentine	↓Sofosbuvir ↓Velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals:		
Efavirenzc	↓Velpatasvir	Coadministration of Sofosbuvir/Velpatasvir with Efavirenz-containing regimens is not recommended.
Regimens containing Tenofovir DF	↑Tenofovir	Monitor for Tenofovir-associated adverse reactions in patients receiving Sofosbuvir/Velpatasvir 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[c]	↑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 10 mg.
Atorvastatin	↑Atorvastatin	Coadministration 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.

DF = Disoproxil Fumarate
a. This table is not all inclusive.
b. ↓ = decrease, ↑ = increase
c. These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with Sofosbuvir/Velpatasvir Based on drug interaction studies conducted with the components of Sofosbuvir or Velpatasvir, no clinically significant drug interactions have been observed with the following drugs

Sofosbuvir/Velpatasvir: Atazanavir/Ritonavir, Cyclosporine, Darunavir/Ritonavir, Dolutegravir, Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide, Emtricitabine, Raltegravir or Rilpivirine

Sofosbuvir: Ethinyl Estradiol/Norgestimate, Methadone, or Tacrolimus

Velpatasvir: Ethinyl Estradiol/Norgestimate, Ketoconazole, or Pravastatin. See Table 3 for use of Sofosbuvir/Velpatasvir with certain HIV antiretroviral regimens

WARNINGS AND PRECAUTIONS

Serious Symptomatic Bradycardia When Sofosbuvir Is Coadministered with Amiodarone and another HCV Direct Acting Antiviral

Coadministration of Amiodarone with Sofosbuvir/Velpatasvir is not recommended. For patients taking Amiodarone who have no other alternative viable treatment options and who will be coadministered Sofosbuvir/Velpatasvir:

- Counsel patients about the risk of symptomatic bradycardia.
- Cardiac monitoring in an in-patient 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 Sofosbuvir/Velpatasvir who need to start Amiodarone therapy due to no other alternative viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to Amiodarone's long half-life, patients discontinuing Amiodarone just prior to starting Sofosbuvir/Velpatasvir should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems.

Risk of Reduced Therapeutic Effect Due to Concomitant Use of Sofosbuvir/Velpatasvir 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 (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.

Risks Associated with Ribavirin and Sofosbuvir/Velpatasvir Combination Treatment

If Sofosbuvir/Velpatasvir is administered with Ribavirin, the warnings and precautions for Ribavirin apply to this combination regimen. Refer to the Ribavirin prescribing information for a full list of the warnings and precautions for Ribavirin

OVERDOSAGE

No specific antidote is available for overdose with Sofosbuvir/Velpatasvir. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir/Velpatasvir consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. 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.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store in cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packing

Sofosvel Tablet

Each commercial box contains 28 tablets in a bottle.

Each commercial box contains 6 tablets in Alu-Alu blister pack.

Manufactured By
BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

For more info:

Only for Export

LF20802