Fosbu V ™

(Sofosbuvir + Velpatasvir)

Highnoon

COMPOSITION
FOSBU V 400mg/100mg Tablet:
Each film-coated tablet contains:
Sofosbuvir 400mg
Velpatasvir 100mg

DESCRIPTION
FOSBU V 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 a NS5A inhibitor.

MECHANISM OF ACTION
FOSBU V (sofosbuvir and velpatasvir) is a fixed-dose combination of sofosbuvir and velpatasvir which are direct-acting antiviral agents against hepatitis C virus.

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.
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.

PHARMACOKINETICS
Sofosbuvir
The peak plasma concentration of sofosbuvir was observed at approximately 0.5-2 hours post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose. 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. Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively. Sofosbuvir can be administered without regard to food.
Velpatasvir
The peak plasma concentration of velpatasvir was observed at approximately 3 hours post-dose, regardless of dose level. Velpatasvir is approximately 99.5% bound to human plasma proteins and is extensively metabolized to CYP2B6, CYP2C8 and CYP3A6. The median terminal half- life of velpatasvir is 3 hours.

INDICATIONS AND USAGE
It is indicated for the treatment of adults and paediatric patients 3 years of age and older with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infections:
- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis for use in combination with ribavirin

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 this combination (sofosbuvir and velpatasvir).

Recommended Dosage
Recommended Treatment Regimen and Duration in Patients 3 Years of Age and Older:
Table 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 sofosbuvir and velpatasvir combination once daily for 12 weeks

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, without cirrhosis and with compensated cirrhosis (Child-Pugh A)	sofosbuvir + velpatasvir for 12 weeks
Treatment-naïve and treatment-experienced, with decompensated cirrhosis (Child-Pugh B or C)	sofosbuvir + velpatasvir + ribavirin for 12 weeks

Recommended Dosage in Adults
The recommended dosage in adults is one tablet (400 mg sofosbuvir and 100 mg velpatasvir) taken orally once daily with or without food. When administered with this combination, 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 haemoglobin and creatinine clearance.

Recommended Dosage in Paediatric Patients 3 Years of Age and Older
The recommended dosage of in paediatric patients 3 years of age and older is based on weight:

Body Weight (kg)	*Sofosbuvir and Velpatasvir Combination* daily dose	Dosing of the Tablet
less than 17	150 mg/37.5 mg per day	N/A
17 to less than 30	200 mg/50 mg per day	one 200 mg/50 mg tablet once daily
at least 30	400 mg/100 mg per day	one 400 mg/100 mg tablet once daily

Recommended Dosing of Ribavirin with Sofosbuvir and Velpatasvir Combination for Pediatric Patients 3 Years and Older

Body Weight (kg)	Oral Ribavirin Daily Dosage
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)

No dosage adjustment of Sofosbuvir and Velpatasvir Combination is recommended in patients with any degree of renal impairment, including patients requiring dialysis.

CONTRAINDICATIONS

The combination (sofosbuvir and velpatasvir) and ribavirin regimen is contraindicated in patients for whom ribavirin is contraindicated. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.

WARNINGS AND PRECAUTIONS

- 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 immunosuppressants 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 this combination (sofosbuvir and 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 this combination (sofosbuvir and velpatasvir) and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

- Cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with a sofosbuvir containing regimen. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen ledipasvir/ sofosbuvir. 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. Coadministration of amiodarone is not recommended. For patients taking amiodarone who have no other alternative viable treatment options and who will be coadministered sofosbuvir and 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 this medicine 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 and 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 pain, confusion, or memory problems.

- 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 and velpatasvir. The use of these agents with sofosbuvir and velpatasvir is not recommended.

- If it is administered with ribavirin, the warnings and precautions for ribavirin apply to this combination regimen.

ADVERSE REACTIONS

The reported adverse reactions are serious symptomatic bradycardia, heart block, headache, fatigue, asthenia, anemia, nausea, insomnia, irritability, diarrhea, rash, depression, decrease in hemoglobin, lipase elevation, creatinine kinase elevation, increases in indirect bilirubin, skin rashes, sometimes with blisters or angioedema-like swelling angioedema, pruritus, chills, decrease appetite, pyrexia, myalgia, Stevens-Johnson syndrome.
If it is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions.

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.
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. It may be coadministered with P-gp, BCRP, and CYP inhibitors.

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

Established and potentially significant drug interactions
Below mentioned table provides a listing of established or potentially clinically significant drug interactions.

Table: Potentially significant drug interactions

Concomitant drug class: Drug name	Effect on Concentration	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 and velpatasvir administration by 4 hours.
H2 -receptor antagonists (e.g., famotidine)		H2 -receptor antagonists may be administered simultaneously with or 12 hours apart from this combination (Sofosbuvir & Velpatasvir) 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, this combination (Sofosbuvir & Velpatasvir) should be administered with food and taken 4 hours before omeprazole 20mg.
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Coadministration of amiodarone with a sofosbuvir containing regimen may result in serious symptomatic bradycardia. Coadminitration of amiodarone with this combination (Sofosbuvir & Velpatasvir) is not recommended.
Digoxin	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when administered with this combination (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 rifampinc rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals: efavirenz	↓ velpatasvir	Coadministration of this combination (Sofosbuvir & Velpatasvir) is not recommended with efavirenz containing regimens.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving this combination (Sofosbuvir & Velpatasvir) concomitantly with a regimen containing tenofovir DF.
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 this combination (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 this combination (Sofosbuvir & Velpatasvir) at a dose that does not exceed 10mg.
atorvastatin	↑ atorvastatin	Coadministration of this combination (Sofosbuvir & Velpatasvir) with atorvastatin may be 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. ↓ = decrease, ↑ = increase.

USE IN SPECIFIC POPULATIONS
Pregnancy
If it 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. No adequate human data are available to establish whether or not sofosbuvir and velpatasvir poses a risk to pregnancy outcomes.

Nursing Mothers
It is not known whether the sofosbuvir and velpatasvir 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 sofosbuvir and velpatasvir and any potential adverse effects on the breastfed child from sofosbuvir and velpatasvir or from the underlying maternal condition.
If it is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen.

Females and Males of Reproductive Potential
If it is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen.

Geriatric Use
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 is warranted in geriatric patients.

Renal Impairment
No dosage adjustment of sofosbuvir and velpatasvir combination is recommended for patients with mild, moderate, or severe 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.

Pediatric Use
The safety and effectiveness of sofosbuvir and velpatasvir combination have not been established in paediatrics patients less than 3 years of age.
For paediatrics patients this combination is indicated, no clinically meaningful differences in pharmacokinetics have been observed in comparison to those observed in adults.
The safety and effectiveness have been comparable to those observed in adults. However, patients less than 6 years of age may have vomiting may spit up the drug.

In patients with severe renal impairment, including those requiring dialysis, exposures of GS-331007, the inactive metabolite of sofosbuvir, are increased.

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 sofosbuvir and velpatasvir and ribavirin.

OVERDOSAGE
No specific antidote is available for overdose. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with 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.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in dry place. Protect from light.

PRESENTATION
FOSBU V 400mg/100mg Tablets:
Alu. Alu Blister Pack of 4 x 7's.

فوسبو وی ™

(سوفوسبوویر + ویلپاٹاسویر)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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