# Fosbu®
(Sofosbuvir)

Highnoon

**COMPOSITION**
**Fosbu 400mg Tablet:**
Each film-coated tablet contains: Sofosbuvir 400mg

**DESCRIPTION**
Sofosbuvir is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.

**MECHANISM OF ACTION**
Sofosbuvir is an 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.

**PHARMACOKINETICS**
The peak plasma concentration of sofosbuvir was observed at approximately 0.5 hour - 2 hours post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 hours 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 hour and 27 hours, respectively. Sofosbuvir can be administered without regard to food.

**INDICATIONS AND USAGE**
It is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection as a component of a combination antiviral treatment regimen:
- genotype 1 or 4 infection without cirrhosis or with compensated cirrhosis for use in combination with pegylated interferon and ribavirin
- genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

Pediatric Patients:
Sofosbuvir is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

**DOSAGE AND ADMINISTRATION**
HBV screening should be performed by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) in all patients before initiation of treatment with Fosbu.

**Recommended Dosage in Adults**
The recommended dosage of Sofosbuvir is one 400 mg tablet, taken orally, once daily with or without food.
Administer Sofosbuvir in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of HCV. The recommended treatment regimen and duration for Sofosbuvir combination therapy is provided in given table. For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in given table.

Recommended Treatment Regimen and Duration in Adult Patients with Genotype 1, 2, 3, or 4 HCV

| | Patient Population | Treatment Regimen and Duration |
|---|---|---|
| Genotype 1 or 4 | Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A) | Sofosbuvir + peginterferon alfa + ribavirin 12 weeks |
| Genotype 2 | Treatment-naive and treatment-experienced* without cirrhosis or with compensated cirrhosis (Child-Pugh A) | Sofosbuvir + ribavirin 12 weeks |
| Genotype 3 | Treatment-naive and treatment-experienced* without cirrhosis or with compensated cirrhosis (Child-Pugh A) | Sofosbuvir + ribavirin 24 weeks |

*Dosage of ribavirin is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg).*

*The daily dosage of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤50 mL/min) require ribavirin dosage reduction; refer to ribavirin tablet prescribing information.*

*`Treatment-experienced patients have failed an interferon-based regimen with or without ribavirin.*

Sofosbuvir in combination with ribavirin for 24 weeks can be considered for chronic hepatitis C patients with genotype 1 infection who are interferon ineligible. Should be used in combination with ribavirin for treatment of chronic hepatitis C in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first.

Dosage reduction of Sofosbuvir is not recommended. If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dosage should be reduced or discontinued, if appropriate, until the adverse reaction abates or decreases in severity.
Refer to the peginterferon alfa and ribavirin prescribing information for additional information about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dosage.
No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73m²) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite

**Recommended Dosage in Pediatric Patients 3 Years of Age and Older with Genotype 2 or 3 HCV**

The recommended treatment regimen, duration, and recommended dosage for Sofosbuvir combination therapy is given in table below.
In pediatric patients with hepatocellular carcinoma awaiting liver transplantation, administer Sofosbuvir in combination with ribavirin for up to 48 weeks or until the time of liver transplantation, whichever occurs first, to prevent post-transplant HCV reinfection.

| | Patient Population | Treatment Regimen and Duration |
|---|---|---|
| Genotype 2 | Treatment-naive and treatment-experienced* without cirrhosis or with compensated cirrhosis (Child-Pugh A) | Sofosbuvir + ribavirin 12 weeks |
| Genotype 3 | Treatment-naive and treatment-experienced* without cirrhosis or with compensated cirrhosis (Child-Pugh A) | Sofosbuvir + ribavirin 24 weeks |

**Treatment-experienced patients have failed an interferon based regimen with or without ribavirin.*

Dosing for Pediatric Patients 3 Years and Older:

| Body Weight (kg) | Sofosbuvir Daily Dose | Dosing of Sofosbuvir Tablets |
|---|---|---|
| at least 35 | 400 mg per day | one 400 mg tablet once daily |
| 17 to less than 35 | 200 mg per day | |
| Less than 17 | 150 mg per day | |

Recommended Dosing for Ribavirin in Combination Therapy with Sofosbuvir 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 |
| 50–65 | 800 mg per day |
| 66–80 | 1000 mg per day |
| greater than 80 | 1200 mg per day |

The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food.

**CONTRAINDICATIONS**
Hypersensitivity to any ingredient or component of the formulation.
Medicinal products that are strong P-glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort). Co-administration will significantly decrease sofosbuvir plasma concentration and could result in loss of efficacy of sofosbuvir.

When used in combination with peginterferon alfa/ribavirin or ribavirin alone, all contraindications to peginterferon alfa and/or ribavirin also apply to Sofosbuvir combination therapy.
Because ribavirin may cause birth defects and fetal death, Sofosbuvir in combination with peginterferon alfa/ribavirin or ribavirin is contraindicated in pregnant women. Women of childbearing potential or their male partners must use an effective form of contraception. Further details please refer to prescribing information of these drugs.

**ADVERSE REACTIONS**
The reported adverse events of sofosbuvir with ribavirin therapy or / and sofosbuvir, ribavirin and peginterferon alfa are:
Nasopharyngitis, decreased haemoglobin, anaemia, decreased appetite, Insomnia, depression, headache, disturbance in attention, dyspnoea, dyspnoea exertional, cough, nausea, abdominal discomfort, dyspepsia, blood bilirubin increased, alopecia, dry skin, pruritus, arthralgia, back pain, muscle spasms, myalgia, fatigue, pyrexia, asthenia, neutropenia, lymphocyte count decreased, platelet count decreased, weight decreased, anxiety, agitation, dizziness, migraine, memory impairment, blurred vision, diarrhoea, vomiting, constipation, dry mouth, gastroesophageal reflux, chills, influenza-like illness, irritability, pain, chest pain, asthenia, pancytopenia, suicidal ideation and suicide, anorexia, skin rashes, sometimes with blisters or angioedema-like swelling, angioedema.
Adverse reactions in paediatric subjects 3 years of age and older maybe be similar to those in adults. Decreased appetite may also present.
Laboratory changes include bilirubin elevation, creatine kinase elevation and lipase elevation.

**DRUG INTERACTIONS**
- Medicinal products that are strong P-gp inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir and thus are contraindicated with sofosbuvir. Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir. Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Co-administration with such medicinal products is not recommended with sofosbuvir. Co-administration of sofosbuvir with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus sofosbuvir may be co-administered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of medicinal products that are substrates of these transporters.
- Coadministration of Sofosbuvir with antimycobacterials (rifabutin or rifapentine) is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir. Coadministration is not recommended.
- Coadministration of Sofosbuvir with HIV protease inhibitors (tipranavir/ritonavir) is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir, coadministration is not recommended.

**WARNINGS AND PRECAUTIONS**
- Pregnancy: Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least 2 effective non-hormonal methods of contraception and have monthly pregnancy tests.
- 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 Sofosbuvir. 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 and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.
- Serious Symptomatic Bradycardia When Coadministered with Amiodarone
  - 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. The mechanism for this effect is unknown.
  - Coadministration of amiodarone with sofosbuvir is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered Sofosbuvir:
    Counsel patients about the risk of serious 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 who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring. Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting Sofosbuvir 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.
- Risks associated with combination treatment because Sofosbuvir is used in combination with other antiviral drugs for treatment of HCV infection, consult the prescribing information for these drugs used in combination with Sofosbuvir. Warnings and Precautions related to these drugs also apply to their use in Sofosbuvir combination treatment.
- Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

**USE IN SPECIFIC POPULATIONS**
**Pregnancy**
Pregnancy Category X: Use with Ribavirin or Peginterferon Alfa/Ribavirin
Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using two forms of effective contraception during treatment with ribavirin and for 6 months after treatment has concluded.
Pregnancy Category B: Sofosbuvir
There are no adequate and well-controlled studies with Sofosbuvir in pregnant women.
**Nursing Mothers**
It is not known whether Sofosbuvir and its metabolites are present in human breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with ribavirin-containing regimens, taking into account the importance of the therapy to the mother.
**Pediatric Use**
The safety, pharmacokinetics, and efficacy of Sofosbuvir in pediatric patients 3 years of age and older with genotype 2 and 3 infection have been established.
The safety and efficacy of Sofosbuvir in pediatric patients 3 years of age and older with compensated cirrhosis is supported by comparable sofosbuvir and GS-331007 exposures between: 1) adults and pediatric patients without cirrhosis and 2) adults without cirrhosis and adults with compensated cirrhosis. Thus, similar efficacy would be expected for pediatric patients with compensated cirrhosis as adults with compensated cirrhosis.
The safety and efficacy of Sofosbuvir have not been established in pediatric patients less than 3 years of age with HCV genotype 2 or 3. The safety and efficacy of Sofosbuvir have not been established in pediatric patients with HCV genotype 1 or 4.
**Geriatric Use**
No dose adjustment of Sofosbuvir is warranted in geriatric patients.
**Renal Impairment**
No dose adjustment of Sofosbuvir is required for patients with mild or moderate renal impairment. The safety and efficacy of Sofosbuvir have not been established in patients with severe renal impairment (eGFR <30mL/min/1.73m²) or end stage renal disease (ESRD) requiring hemodialysis. No dose recommendation can be given for patients with severe renal impairment or ESRD.
**Hepatic Impairment**
No dose adjustment of Sofosbuvir is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of Sofosbuvir have not been established in patients with decompensated cirrhosis.
**Patients with HCV/HIV-1 Co-infection**
The safety profile of sofosbuvir and ribavirin in HCV/HIV co-infected adult patients was similar to that observed in mono-infected HCV patients treated with sofosbuvir and ribavirin. Sofosbuvir was studied in HCV-infected adult subjects with hepatocellular carcinoma prior to undergoing liver transplantation. The safety profile of sofosbuvir and ribavirin in HCV infected adult patients prior to liver transplantation was similar to that observed in patients treated with sofosbuvir and ribavirin.
**Post-Liver Transplant Patients**
The safety and efficacy of Sofosbuvir have not been established in post-liver transplant patients.
**Patients with Genotype 5 or 6 HCV Infection**
Available data on subjects with genotype 5 or 6 HCV infection are insufficient for dosing recommendations.

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

**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 400mg Tablets**: Alu. Alu. Blister Pack of 4 x 7's.

# فوسبو®
(سوفوسبووير)

**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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Item Code No.14003052