# Hepcee™

Sofosbuvir

**Composition:**

**Hepcee™** Tablet: Each film coated tablet contains Sofosbuvir INN 400 mg.

**Description:**

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.

*Mechanism of Action*

In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with IC50 values ranging from 0.7 to 2.6 μM. GS - 461203 is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

**Indications and Usage:**

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.

- Sofosbuvir efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

The following points should be considered when initiating treatment with Sofosbuvir:

- Monotherapy of Sofosbuvir is not recommended for treatment of CHC.
- Treatment regimen and duration are dependent on both viral genotype and patient population.
- Treatment response varies based on baseline host and viral factor.

**Dosage and Administration:**

*Recommended Dose in Adults*

The recommended dose of Sofosbuvir is one 400 mg tablet, taken orally, once daily with or without food.

Sofosbuvir should be used in combination with Ribavirin or in combination with pegylated Interferon and Ribavirin for the treatment of CHC in adults. The recommended regimen and treatment duration for

Sofosbuvir combination therapy is provided in Table 1.

*Table 1: Recommended Regimens and Treatment Duration for Sofosbuvir Combination Therapy in HCV Mono-infected and HCV/HIV-1 Co-infected Patients*

| | Treatment | Duration |
|---|---|---|
| Patients with genotype 1 or 4 CHC | Sofosbuvir + Peginterferon alfa + Ribavirin | 12 weeks |
| Patients with genotype 2 CHC | Sofosbuvir + Ribavirin | 12 weeks |
| Patients with genotype 3 CHC | Sofosbuvir + Ribavirin | 24 weeks |

Sofosbuvir in combination with Ribavirin for 24 weeks can be considered as a therapeutic option for CHC patients with genotype 1 infection who are ineligible to receive an Interferon-based regimen. Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient.

*Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation*

Sofosbuvir in combination with Ribavirin is recommended for up to 48 weeks or until the time of liver transplantation, whichever occurs first, to prevent post-transplant HCV reinfection.

*Dose Modification*

Genotype 1 and 4:

If a patient has a serious adverse reaction potentially related to Peginterferon alfa and/or Ribavirin, the Peginterferon alfa and/or Ribavirin dose should be reduced or discontinued. 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 dose.

Genotype 2 and 3:

If a patient has a serious adverse reaction potentially related to Ribavirin, the Ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 2 provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

*Table 2: Ribavirin Dose Modification Guideline for Coadministration with Sofosbuvir*

| Laboratory Values | Reduce Ribavirin Dose to 600 mg/day if: | Discontinue Ribavirin if: |
|---|---|---|
| Hemoglobin in patients with no cardiac disease | <10 g/dL | <8.5 g/d |
| Hemoglobin in patients with history of stable cardiac disease | ≥2 g/dL decrease in hemoglobin during any 4 week treatment period | <12 g/dL despite 4 weeks at reduced dose |

a. The daily dose of Ribavirin is administered orally in two divided doses with food.

b. Once Ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart Ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that Ribavirin be increased to the original assigned dose (1000 mg to 1200 mg daily).

*Discontinuation of Dosing*

If the other agents used in combination with Sofosbuvir are permanently discontinued, Sofosbuvir should also be discontinued.

*Severe Renal Impairment and End Stage Renal Disease*

No dose recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m$^2$) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

**Contraindications:**

When Sofosbuvir is used in combination with Ribavirin or Peginterferon alfa/Ribavirin, the contraindications applicable to those agents are applicable to combination therapies. Refer to the prescribing information of Peginterferon alfa and Ribavirin for a list of their contraindications.

Sofosbuvir combination treatment with Ribavirin or Peginterferon alfa/Ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant because of the risks for birth defects and fetal death associated with Ribavirin.

**Warnings and Precautions:**

*Serious Symptomatic Bradycardia When Coadministered with Amiodarone and Another HCV Direct Acting Antiviral*

Coadministration of amiodarone with Sofosbuvir in combination with another direct acting antiviral (DAA) is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered Sofosbuvir and another DAA:

- 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 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.

*Pregnancy: Use with Ribavirin or Peginterferon Alfa/Ribavirin*

Ribavirin may cause birth defects and/or death of the exposed fetus and animal studies have shown that Interferons have abortifacient effects. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

When Sofosbuvir is used in combination with Ribavirin or Peginterferon alfa/Ribavirin, women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time.

*Use with Potent P-gp Inducers*

Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease Sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of Sofosbuvir. Rifampin and St. John's wort should not be used with Sofosbuvir.

**Adverse Reactions:**

The most common adverse events (incidence greater than or equal to 20%, all grades) observed with Sofosbuvir in combination with Ribavirin were fatigue and headache. The most common adverse events observed with Sofosbuvir in combination with Peginterferon alfa and Ribavirin were fatigue, headache, nausea, insomnia, anemia, pruritus, asthenia, rash, decreased appetite, chills, influenza like illness, pyrexia, diarrhea, neutropenia, myalgia, irritability.

**Drug Interactions:**

*Potential for Drug Interactions*

After oral administration of Sofosbuvir, Sofosbuvir is rapidly converted to the predominant circulating metabolite GS-331007 that accounts for greater than 90% of drug related material systemic exposure, while the parent sofosbuvir accounts for approximately 4% of drug related material. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses. Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Drugs that are potent P-gp inducers in the intestine (e.g., rifampin or St.John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir and thus should not be used with Sofosbuvir. Coadministration of Sofosbuvir with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration; accordingly, Sofosbuvir may be coadministered 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 drugs that are substrates of these transporters.The intracellular metabolic activation pathway of Sofosbuvir is mediated by generally low affinity and high capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant drugs.

*Potentially Significant Drug Interactions*

The following classes of drugs are found to be potential for drug interactions that may occur with Sofosbuvir: Antiarrythmics: amiodarone; Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine; Antimycobacterials: rifabutin, rifampin, rifapentine; Herbal Supplements: St. John's wort (Hypericum perforatum); HIV Protease Inhibitors: tipranavir/ritonavir.

*Manufactured by:*

**Julphar Bangladesh Ltd.**

Sreepur, Gazipur, Bangladesh.

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**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. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats, without effect on nursing pups. 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*

Safety and effectiveness of Sofosbuvir in children less than 18 years of age have not been established.

*Geriatric Use*

Sofosbuvir was administered to 90 subjects aged 65 and over. The response rates observed for subjects over 65 years of age were similar to that of younger subjects across treatment groups. 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<30 mL/min/1.73m$^2$) 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 and efficacy of Sofosbuvir was assessed in 223 HCV/HIV-1 co-infected subjects. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects.

*Post-Liver Transplant Patients*

The safety and efficacy of Sofosbuvir have not been established in post-liver transplant patients.

*CHC 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:**

The highest documented dose of Sofosbuvir was a single supratherapeutic dose of Sofosbuvir 1200 mg administered to 59 healthy subjects. In that trial, there were no untoward effects observed at this dose level, and adverse events were similar in frequency and severity to those reported in the placebo and Sofosbuvir 400 mg treatment groups. The effects of higher doses are not known.
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. A 4-hour hemodialysis session removed 18% of the administered dose.

**How Supplied/Storage and Handling:**

**Hepcee™** tablets are caplet-shaped, film-coated tablets containing 400 mg Sofosbuvir. Each plastic container contains 7/28 tablets, a silica gel desiccant and is closed with a child-resistant closure. Store at room temperature below 30°C (86°F).

- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing

*Manufactured by:*
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Sreepur, Gazipur, Bangladesh.