SOFHEP™ Tablets
(Sofosbuvir)

سوف ہیپ ٹیبلیٹس

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:
Sofosbuvir…..400mg

CLINICAL PARTICULARS
Therapeutic Indications
Adult Patients:
SOFHEP (Sofosbuvir) is indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen in adults.
- 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:
SOFHEP is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated 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 SOFHEP.

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

Table 1: 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	Sofhep + peginterferon alfa[a] + ribavirin[b] 12 weeks
Genotype 2	Treatment-naïve and treatment-experienced[c] without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Sofhep + ribavirin[b] 12 weeks
Genotype 3	Treatment-naïve and treatment-experienced[c] without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Sofhep + ribavirin[b] 24 weeks

a. See peginterferon alfa prescribing information for dosage recommendation for patients with genotype 1 or 4 HCV.
b. Dosage of ribavirin is weight-based (<75 kg = 1000mg 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 prescribing information.
c.Treatment-experienced patients have failed an interferon based regimen with or without ribavirin.

Patients with Genotype 1 HCV Who are Ineligible to Receive an Interferon-Based Regimen
SOFHEP in combination with ribavirin for 24 weeks can be considered as a therapeutic option for 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
Administer SOFHEP 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.
Recommended Dosage in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg
The recommended dosage of SOFHEP in pediatric patients 12 years of age and older or weighing at least 35 kg is one 400 mg tablet taken orally once daily with or without food in combination with ribavirin.

The recommended treatment regimen and duration for SOFHEP combination therapy is provided in Table 2. Table 3 provides the weight-based dosage of ribavirin when used in combination with SOFHEP for pediatric patients. For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 2 and Table 3. Refer to Drug Interactions (7) for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 2: Recommended Treatment Regimen and Duration in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg

	Patient Population	Treatment Regimen And Duration
Genotype 2	Treatment-naïve and treatmentexperienceda without cirrhosis or with compensated cirrhosis (Child-Pugh A)	SOFHEP + ribavirin[b] 12 weeks
Genotype 3	Treatment-naïve and treatmentexperienceda without cirrhosis or with compensated cirrhosis (Child-Pugh A)	SOFHEP + ribavirin[b] 24 weeks

a. Treatment-experienced patients have failed an interferon based regimen with or without ribavirin
b. See Table 3 for weight-based ribavirin dosing recommendations

Table 3: Recommended Dosing for Ribavirin in Combination Therapy with SOFHEP for Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg

Body Weight kg	Ribavirin Daily Dosage[a]
less than 47	15 mg/kg/day
47–49	600 mg/day
50–65	800 mg/day
66–80	1000 mg/day
greater than 80	1200 mg/day

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

Dosage Modification
Dosage reduction of SOFHEP 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.
Discontinuation of Dosing
If the other agents used in combination with SOFHEP are permanently discontinued, SOFHEP should also be discontinued.
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/1.73m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

Special Populations
Elderly
No dose adjustment is required for elderly patients.
Pediatric population
The safety and efficacy of SOFHEP have not been established in pediatric patients less than 12 years of age and weighing less than 35 kg with HCV genotype 2 or 3. The safety and efficacy of SOFHEP have not been established in pediatric patients with HCV genotype 1 or 4.
Renal impairment
No dose adjustment of Sofhep (Sofosbuvir) is required for patients with mild or moderate renal impairment.
Hepatic impairment
No dose adjustment of Sofhep (Sofosbuvir) is required for patients with mild, moderate or severe hepatic impairment.

CONTRAINDICATIONS
- Sofosbuvir is contraindicated in patients with known hypersensitivity to sofosbuvir or to any excipient of the product.
- When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, the contraindications applicable to those agents are applicable to combination therapies.

WARNINGS AND PRECAUTIONS
Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV
Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.
Serious Symptomatic Bradycardia When Coadministered with Amiodarone
Serious symptomatic bradycardia may occur in patients taking amiodarone with a

sofosbuvir-containing regimen, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with SOFHEP is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended.

Risk of Reduced Therapeutic Effect Due to Use with P-gp Inducers

Drugs that are 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 SOFHEP. The use of rifampin and St. John's wort with SOFHEP is not recommended.

Risks Associated with Combination Treatment

Because SOFHEP is used in combination with other antiviral drugs for treatment of HCV infection, consult the prescribing information for these drugs used in combination with SOFHEP. Warnings and Precautions related to these drugs also apply to their use in SOFHEP combination treatment.

INTERACTIONS

P-gp inducers

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.

Antiarrhythmics

Co-administration of amiodarone with sofosbuvir in combination with another direct acting antiviral is not recommended; as such combination may result in serious symptomatic bradycardia. If co-administration is required, cardiac monitoring is recommended.

Anticonvulsants

Co-administration of sofosbuvir with carbamazepine, phenytoin,phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.

Antimycobacterials

Co-administration of sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended. Sofosbuvir should not be used with rifampin.

HIV Protease Inhibitors

Co-administration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.

Analeptics

Co-administration of sofosbuvir with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.

PREGNANCY AND BREAST FEEDING

When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, extreme caution must be taken to 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 methods of contraception and have monthly pregnancy tests.

It is unknown whether sofosbuvir and its metabolites are excreted in human milk. Because of the potential for adverse reactions from the drug in nursing infants, sofosbuvir should not be used during breast feeding.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE

Sofosbuvir has moderate influence on the ability to drive and use machine.

Patients should be cautioned about the risk of an influence on their ability to drive a car and operate machinery.

ADVERSE REACTIONS

The following adverse reactions have been reported during treatment with sofosbuvir:

Sofosbuvir + Ribavirin

Very common:

Hemoglobin decreased, insomnia, headache, nausea, blood bilirubin increased, fatigue and irritability

Common:

Nasopharyngitis, anemia, depression, disturbance in attention, dyspnea, dyspnea exertional, cough, abdominal discomfort, constipation, dyspepsia, alopecia, dry skin, pruritus, arthralgia, back pain, muscle spasms, myalgia pyrexia and asthenia.

Sofosbuvir + Ribavirin + Peginterferon alfa

Very common:

Anemia, neutropenia, lymphocyte count decreased, platelet count decreased, decreased appetite, insomnia, dizziness, headache, dyspnea, cough, diarrhea, nausea, vomiting, blood bilirubin increased, rash, pruritus, arthralgia, myalgia, chills, fatigue, influenza-like illness, irritability, pain and pyrexia.

Common:

Weight decreased, depression, anxiety, agitation, migraine, memory impairment, disturbance in attention, vision blurred, dyspnea exertional, constipation, dry mouth, gastroesophageal reflux, alopecia, dry skin, back pain, muscle spasms, chest pain and asthenia.

OVERDOSE

The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1200mg, there were no untoward effects observed at this dose level.

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.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus.

It 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.

Pharmacokinetic Properties

Absorption

Following oral administration sofosbuvir was absorbed with a peak plasma concentration observed at ~0.5-2 hour post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose.

Effect of Food

Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold but it did not substantially affect the sofosbuvir C_{max} or $AUC_{0\text{-inf}}$. The exposure of GS-331007 was not altered in the presence of a high-fat meal. Therefore, sofosbuvir can be administered without regard to food.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1µg/mL to 20µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400mg dose of [^{14}C]-sofosbuvir in healthy individuals, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Metabolism

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.*

Elimination

Following a single 400mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose 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. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

SPECIAL POPULATIONS

Renal impairment

The pharmacokinetics of sofosbuvir were studied in HCV negative patients. Relative to subjects with normal renal function, the sofosbuvir $AUC_{0\text{-inf}}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment. Sofosbuvir $AUC_{0\text{-inf}}$ was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when sofosbuvir was dosed 1 hour after hemodialysis.

Hepatic impairment

The pharmacokinetics of sofosbuvir were studied in HCV-infected patients.Relative to subjects with normal hepatic function, the sofosbuvir $AUC_{0\text{-}24}$ were 126% and 143% higher in moderate and severe hepatic impairment.

PHARMACEUTICAL PARTICULARS

Shelf life

Observe expiry date on the outer pack.

Dosage & Instructions:

As prescribed by the Physician. For details see enclosed leaflet.

Keep out of the reach of children. Protect from sunlight and moisture.

Do not store above 30˚C. Do not use if seal over bottle is broken.

To be sold on the prescription of a registered medical practitioner only.

خوراک و ہدایات :

ڈاکٹری ہدایت کے مطابق استعمال کریں۔ تفصیلات کے لئے اندر موجود معلوماتی پرچہ ملاحظہ فرمائیں۔

بچوں کی پہنچ سے دور رکھیں۔ دھوپ اور نمی سے محفوظ رکھیں۔ ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔

بوتل کی سیل کھلی ہوئی ہو تو استعمال نہ کریں۔ صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Nature and Contents of Container

SOHEP (Sofosbuvir) Tablets 400mg are available in a HDPE bottle pack of 28's.

Manufactured by:

ASPIN
An OBS Group Company
Aspin Pharma (Pvt) Ltd.
Plot No. 10 & 25, Sector No. 20,
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