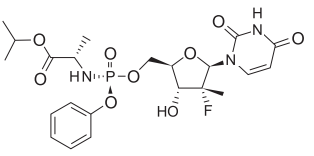
Hepaldi Tablets*

ہیپالڈی ٹیبلٹس

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with HEPALDI. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

COMPOSITION: ***Each film coated tablet contains:*** Sofosbuvir* 400 mg

DESCRIPTION: Sofosbuvir (HEPALDI) is a nucleotide analog inhibitor of HCV NS5B polymerase. The IUPAC name for Sofosbuvir is (*S*)-Isopropyl 2-(((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



Sofosbuvir is a white to off-white crystalline solid with a solubility of ≥ 2 mg/mL across the pH range of 2-7.7 at 37 °C and is slightly soluble in water.

Sofosbuvir (HEPALDI) tablets are for oral administration

PHARMACOLOGY: ***Mechanism of Action:*** Sofosbuvir is a direct-acting antiviral agent (DAA) against the hepatitis C virus. It is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. ***Pharmacodynamics:*** *Cardiac Electrophysiology:* Sofosbuvir does not prolong QT interval to any clinically relevant extent. ***Pharmacokinetics:*** *Absorption:* Sofosbuvir and its major metabolite (GS-331007) AUCs are near dose proportional over the dose range of 200 mg to 1200 mg. *Effect of Food:* Sofosbuvir (HEPALDI) 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 1 microgram/mL to 20 microgram/mL. Protein binding of major metabolite (GS-331007) is minimal in human plasma. After a single 400 mg dose of Sofosbuvir, the blood to plasma ratio of Sofosbuvir is approximately 0.7. *Metabolism:* Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate. 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 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. After a single 400 mg oral dose of Sofosbuvir, Sofosbuvir and its major metabolite (GS-331007) accounts for approximately 4% and greater than 90% of drug related material. *Elimination:* The majority of the Sofosbuvir dose that recovers in urine is major metabolite 78% while Sofosbuvir is 3.5%. Renal clearance is the major elimination pathway for major metabolite (GS-331007). The median terminal half-lives of Sofosbuvir and major metabolite (GS-331007) are 0.4 and 27 hours, respectively.

INDICATIONS: Sofosbuvir (HEPALDI) is indicated for the treatment of genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection as a component of a combination antiviral treatment regimen.

CONTRAINDICATIONS: When Sofosbuvir (HEPALDI) is used in combination with ribavirin or peginterferon alfa/ribavirin, the contraindications applicable to those agents are applicable to combination therapies.

POSSIBLE ADVERSE EFFECTS: The following serious adverse effects are described below:

- Serious symptomatic bradycardia when coadministered with amiodarone and another HCV direct acting antiviral (DAA).
- The most common adverse events for Sofosbuvir (HEPALDI) + ribavirin combination therapy are fatigue and headache. The most common adverse events for Sofosbuvir (HEPALDI) + peginterferon alfa + ribavirin combination therapy are fatigue, headache, nausea, insomnia and anemia.
- With the exception of anemia and neutropenia, the majority of events presented below may occur at severity of grade 1 in Sofosbuvir (HEPALDI)-containing regimens:

Fatigue, headache, nausea, insomnia, pruritus, anemia, asthenia, rash, decreased appetite, chills, influenza like illness, pyrexia, diarrhea, neutropenia, myalgia and irritability.

Less Common Adverse Effects (less than 1%): The following adverse reactions may occur in less than 1% of patients receiving Sofosbuvir (HEPALDI) in a combination regimen.

Hematologic Effects: Pancytopenia (particularly in patients receiving concomitant pegylated interferon).

Psychiatric Disorders: Severe depression (particularly in patients with pre-existing history of psychiatric illness), including suicidal ideation and suicide.

Laboratory Abnormalities: Changes in selected hematological parameters are as follows:

Hemoglobin: <8.5 - <10 g/dL may be observed in patients who are taking Sofosbuvir (HEPALDI) + ribavirin for 12 to 24 weeks and Sofosbuvir (HEPALDI) + peginterferon alfa + ribavirin for 12 weeks.

Neutrophils: <0.5 - <0.75 x109/L may be observed in patients who are taking Sofosbuvir (HEPALDI) + ribavirin for 12 to 24 weeks and Sofosbuvir (HEPALDI) + peginterferon alfa + ribavirin for 12 weeks.

Platelets: ≥25 - <50 x109/L may be observed in patients who are taking Sofosbuvir (HEPALDI) + ribavirin for 12 to 24 weeks and Sofosbuvir (HEPALDI) + peginterferon alfa + ribavirin for 12 weeks.

Bilirubin Elevations: Bilirubin levels may peak during the first 1 to 2 weeks of treatment and subsequently decrease and return to baseline levels by post-treatment Week 4.

Creatine Kinase Elevations: Isolated, asymptomatic creatine kinase elevation may occur in patients taking peginterferon alfa + ribavirin for 24 weeks, Sofosbuvir (HEPALDI) + peginterferon alfa + ribavirin for 12 weeks and Sofosbuvir (HEPALDI) + ribavirin for 12 weeks.

Lipase Elevations: Isolated, asymptomatic lipase elevation may occur in patients taking Sofosbuvir (HEPALDI) + peginterferon alfa + ribavirin for 12 weeks, Sofosbuvir (HEPALDI) + ribavirin for 12 weeks and Sofosbuvir (HEPALDI) + ribavirin 24 weeks and peginterferon alfa + ribavirin for 24 weeks.

DRUG INTERACTIONS: Sofosbuvir is a substrate of drug transporter P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) while the predominant circulating major metabolite (GS-331007) is not. Drugs that are 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 (HEPALDI), and thus concomitant use with Sofosbuvir (HEPALDI) is not recommended. Information on potential drug interactions with Sofosbuvir (HEPALDI) is summarized in Table 01. The table is not all-inclusive.

Table 01

Potentially Significant Drug Interactions:

Alteration in Dosage or Regimen May Be Recommended Based on Drug Interaction or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: amiodarone	Effect on amiodarone and Sofosbuvir concentrations unknown	Coadministration of amiodarone with Sofosbuvir (HEPALDI) in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with Sofosbuvir (HEPALDI) in combination with another DAA is not recommended; if coadministration is required, cardiac monitoring is recommended.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ Sofosbuvir + its major metabolite (GS-331007)	Coadministration of Sofosbuvir (HEPALDI) with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of Sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir (HEPALDI). Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin rifapentine	↓ Sofosbuvir + its major metabolite (GS-331007)	Coadministration of Sofosbuvir (HEPALDI) with rifabutin or rifapentine is expected to decrease the concentration of Sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir (HEPALDI). Coadministration is not recommended. Coadministration of Sofosbuvir (HEPALDI) with rifampin, an intestinal P-gp inducer is not recommended.
Herbal Supplements: St. John's wort (*Hypericum perforatum*)	↓ Sofosbuvir + its major metabolite (GS-331007)	Coadministration of Sofosbuvir (HEPALDI) with St. John's wort, an intestinal P-gp inducer is not recommended.
HIV Protease Inhibitors: tipranavir/ritonavir	↓ Sofosbuvir + its major metabolite (GS-331007)	Coadministration of Sofosbuvir (HEPALDI) with tipranavir/ritonavir is expected to decrease the concentration of Sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir (HEPALDI). Coadministration is not recommended.

a. This table is not all-inclusive.
b. ↓ = decrease.

USE IN SPECIFIC POPULATIONS: ***Pregnancy:*** *Pregnancy Category B:* Sofosbuvir (HEPALDI) should be used during pregnancy only if the potential for benefit justifies the potential risk to the fetus. If Sofosbuvir (HEPALDI) is administered with ribavirin or peginterferon and ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. ***Nursing Mothers:*** It is not known whether Sofosbuvir (HEPALDI) and its metabolites are present in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sofosbuvir (HEPALDI) and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. If Sofosbuvir (HEPALDI) is administered in a regimen containing ribavirin, the information for ribavirin with regard to nursing mothers also applies to this combination regimen. ***Pediatric Use:*** Safety and effectiveness of Sofosbuvir (HEPALDI) in children less than 18 years of age have not been established. ***Geriatric Use:*** No dosage adjustment of Sofosbuvir (HEPALDI) is warranted in geriatric patients. ***Renal Impairment:*** No dosage adjustment of Sofosbuvir (HEPALDI) is required for patients with mild or moderate renal impairment. The safety and efficacy of Sofosbuvir (HEPALDI) have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m^2) or ESRD requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD. ***Hepatic Impairment:*** No dosage adjustment of Sofosbuvir (HEPALDI) is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of Sofosbuvir (HEPALDI) have not been established in patients with decompensated cirrhosis. ***Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation:*** HCV-infected patients, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria (defined as the presence of a tumor 5 cm or less in diameter in patients with single hepatocellular carcinoma and no more than three tumor nodules, each 3 cm or less in diameter in patients with multiple tumors and no extrahepatic manifestations of the cancer or evidence of vascular invasion of tumor) can be given 400 mg Sofosbuvir (HEPALDI) and weight-based 1000-1200 mg ribavirin daily for 24-48 weeks or until the time of liver transplantation, whichever occurred first. ***Post-Liver Transplant Patients:*** The safety and efficacy of Sofosbuvir (HEPALDI) have not been established in post-liver transplant patients. ***Patients with Genotype 5 or 6 HCV Infection:*** Available data on patients with genotype 5 or 6 HCV infection are insufficient for dosing recommendations.

WARNINGS: ***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 (HEPALDI). 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 (HEPALDI) and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. ***Serious Symptomatic Bradycardia When Coadministered with Amiodarone and another HCV Direct Acting Antiviral (DAA):*** Patients 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 resolves after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with Sofosbuvir (HEPALDI) 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 (HEPALDI) 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.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting Sofosbuvir (HEPALDI) in combination with a DAA should also undergo similar cardiac monitoring as outlined above.

Risk of Reduced Therapeutic Effect Due to Use with P-glycoprotein (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 Sofosbuvir (HEPALDI). The use of rifampin and St. John's wort with Sofosbuvir (HEPALDI) is not recommended. ***Risks Associated with Combination Treatment:*** Because Sofosbuvir (HEPALDI) 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 (HEPALDI). Warnings and Precautions related to these drugs also apply to their use in Sofosbuvir (HEPALDI) combination treatment. ***Related Products Not Recommended:*** The use of Sofosbuvir (HEPALDI) with other products containing Sofosbuvir is not recommended.

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 Sofosbuvir (HEPALDI). ***Recommended Dosage:*** The recommended dosage of Sofosbuvir (HEPALDI) is one 400 mg tablet, taken orally, once daily with or without food. Administer Sofosbuvir (HEPALDI) 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 (HEPALDI) combination therapy are provided in Table 02.

Table 02

Recommended Treatment Regimens and Duration:

Patient Population	*Treatment Regimen*	*Duration*
Genotype 1 or 4	Sofosbuvir (HEPALDI) + peginterferon alfa[a] + ribavirin[b]	12 weeks
Genotype 2	Sofosbuvir (HEPALDI) + ribavirin[b]	12 weeks
Genotype 3	Sofosbuvir (HEPALDI) + 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 = 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 prescribing information.

Patients with Genotype 1 HCV Who are Ineligible to Receive an Interferon-Based Regimen: Sofosbuvir (HEPALDI) 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 Sofosbuvir (HEPALDI) 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. ***Dosage Modification:*** Dosage reduction of Sofosbuvir (HEPALDI) 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. ***Discontinuation of Dosing:*** If the other agents used in combination with Sofosbuvir (HEPALDI) are permanently discontinued, Sofosbuvir (HEPALDI) should also be discontinued.

SPECIAL INSTRUCTION TO THE PHYSICIAN: ***Overdosage:*** The highest documented dosage of Sofosbuvir is a single dose of Sofosbuvir 1200 mg (three times the recommended dosage). The effects of higher dosages are not known. No specific antidote is available for overdose with Sofosbuvir (HEPALDI). If overdose occurs, the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir (HEPALDI) 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 removes 18% of the administered dose.

STORAGE: Store in a cool, dry and dark place below 30 °C. Keep out of the reach of children.

PRESENTATION: HEPALDI 400 mg film coated tablets are available in a packing containing 28 tablets.

PRECAUTIONS: To be sold and used on the prescription of registered medical practitioners (RMPs) only.
*Scotmann Specs.

خوراک: رجسٹرڈ میڈیکل پریکٹشنرز کی ہدایت کے مطابق۔

احتیاط: ٹھنڈی، خشک اور تاریک جگہ پر 30 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔

بچوں کی پہنچ سے دور رکھیں۔

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