℞ **SOFOSBUVIR**
CAPRIBUVIR
400 mg film-coated tablet
Direct Acting Antiviral

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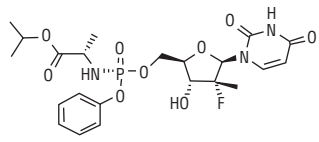
FORMULATION:

Sofosbuvir Tablets 400 mg: Each film-coated tablet contains Sofosbuvir 400 mg.

DRUG DESCRIPTION

Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase.

The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-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 tablets are for oral administration. Each film - coated tablet contains Sofosbuvir 400 mg. The tablets include the following inactive ingredients: Mannitol (Pearlitol 160C) Microcrystalline Cellulose (Avicel PH 102), Croscarmellose sodium (Ac-Di-Sol), Colloidal Silicon dioxide (Aerosil 200), Magnesium stearate (Ligamed MF-2-V), Opadry II orange 85F530007 and Purified water.

THERAPEUTIC INDICATIONS

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 factors

POSOLOGY AND METHOD OF 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 below Table.

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[a] + ribavirin[b]	12 weeks
Patients with genotype 2 CHC	Sofosbuvir + ribavirin[b]	12 weeks
Patients with genotype 3 CHC	Sofosbuvir + ribavirin[b]	24 weeks

a See peginterferon alfa prescribing information for dosing recommendation for patients with genotype 1 or 4 CHC.

b Dose of ribavirin is weight-based (<75 kg = 1000 mg and ≥ 75 kg = 1200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤ 50 mL/min) require ribavirin dose reduction; refer to ribavirin prescribing information.

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

Dose reduction of Sofosbuvir is not recommended.

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. Below Table provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

Ribavirin Dose Modification Guideline for Coadministration with Sofosbuvir

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day[a] If:	Discontinue Ribavirin If[b]:
Hemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
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.

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

Drug interaction information for sofosbuvir with potential concomitant drugs is summarized in below Table. The drug interactions described are based on potential drug interactions that may occur with sofosbuvir. The table is not all-inclusive.

Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies 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 in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with Sofosbuvir in combination with another DAA is not recommended; if coadministration is required, cardiac monitoring is recommended.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓sofosbuvir ↓GS-331007	Coadministration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin rifapentine	↓sofosbuvir ↓GS-331007	Coadministration of Sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended. sofosbuvir should not be used with rifampin, a potent intestinal P-gp inducer.
Herbal Supplements: St. John's wort (Hypericum perforatum)	↓sofosbuvir ↓GS-331007	Sofosbuvir should not be used with St. John's wort, a potent intestinal P-gp inducer.
HIV Protease Inhibitors: tipranavir/ritonavir	↓sofosbuvir ↓GS-331007	Coadministration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

a. This table is not all inclusive.

b. ↓ = decrease.

Drugs without Clinically Significant Interactions with sofosbuvir

In addition to the drugs included in above table, the interaction between sofosbuvir and the following drugs was evaluated in clinical trials and no dose adjustment is needed for either drug: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, oral contraceptives, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

WARNINGS AND PRECAUTIONS

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

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with Sofosbuvir in combination with an investigational agent (NS5A inhibitor) or simeprevir. A fatal cardiac arrest was reported in a patient receiving a sofosbuvir-containing regimen (HARVONI (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 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 are taking Sofosbuvir in combination with another DAA 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 in combination with a DAA 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.

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. Refer also to the prescribing information for ribavirin.

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.

PREGNANCY AND LACTATION

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.

In case of exposure during pregnancy, a Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment.

Animal Data

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans.

Pregnancy Category B: sofosbuvir

There are no adequate and well-controlled studies with sofosbuvir in pregnant women.

Animal Data

No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure to the predominant circulating metabolite GS-331007 increased over the course of gestation from approximately 5- to 10-fold and 12- to 28-fold the exposure in humans at the recommended clinical dose, respectively.

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. See also the prescribing information for ribavirin.

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. Refer also to ribavirin and peginterferon alfa prescribing information for patients with CrCl <50 mL/min.

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. See peginterferon alfa prescribing information for contraindication in hepatic decompensation.

Patients with HCV/HIV-1 Co-infection

The safety and efficacy of sofosbuvir was assessed in 223 HCV/HIV-1 co-infected subjects for dosing recommendations in HCV/HIV-1 co-infected patients. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. Elevated total bilirubin (grade 3 or 4) was observed in 30/32 (94%) subjects receiving atazanavir as part of the antiretroviral regimen. None of the subjects had concomitant transaminase increases. Among subjects not taking atazanavir, grade 3 or 4 elevated total bilirubin was observed in 2 (1.5%) subjects, similar to the rate observed with HCV mono-infected subjects receiving sofosbuvir + ribavirin in Phase 3 trials.

Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation

Sofosbuvir was studied in HCV-infected subjects with hepatocellular carcinoma prior to undergoing liver transplantation in an open-label clinical trial evaluating the safety and efficacy of sofosbuvir and ribavirin administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the trial was post-transplant virologic response (pTVR) defined as HCV RNA < lower limit of quantification (LLOQ) at 12 weeks post-transplant. HCV-infected subjects, 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 carcinomas 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) received 400 mg sofosbuvir and weight-based 1000-1200 mg ribavirin daily for 24-48 weeks or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 subjects who received sofosbuvir and ribavirin; 45 subjects had HCV genotype 1; 44 subjects had a baseline CPT score less than 7 and all subjects had a baseline unadjusted MELD score ≤14. Of these 61 subjects, 41 subjects underwent liver transplantation following up to 48 weeks of treatment with sofosbuvir and ribavirin; 37 had HCV RNA < LLOQ at the time of transplantation. Of the 37 subjects, the post-transplant virologic response (pTVR) rate is 64% (23/36) in the 36 evaluable subjects who have reached the 12 week post-transplant time point. The safety profile of sofosbuvir and ribavirin in HCV-infected subjects prior to liver transplantation was comparable to that observed in subjects treated with sofosbuvir and ribavirin in Phase 3 clinical trials.

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Sofosbuvir has moderate influence on the ability to drive and use machines. Patients should be informed that fatigue and disturbance in attention, dizziness and blurred vision have been reported during treatment with sofosbuvir in combination with peginterferon alfa and ribavirin.

SIDE EFFECTS

Adverse Reactions from Clinical Trials Experience

Sofosbuvir should be administered with ribavirin or peginterferon alfa/ribavirin. Refer to the prescribing information of peginterferon alfa and ribavirin for a description of adverse reactions associated with their use.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of sofosbuvir is based on pooled Phase 3 clinical trial data (both controlled and uncontrolled) including 650 subjects who received sofosbuvir + ribavirin (RBV) combination therapy for 12 weeks, 98 subjects who received sofosbuvir + ribavirin combination therapy for 16 weeks, 250 subjects who received sofosbuvir + ribavirin combination therapy for 24 weeks, 327 subjects who received sofosbuvir + peginterferon (Peg-IFN) alfa + ribavirin combination therapy for 12 weeks, 243 subjects who received peginterferon alfa + ribavirin for 24 weeks and 71 subjects who received placebo (PBO) for 12 weeks.

The proportion of subjects who permanently discontinued treatment due to adverse events was 4% for subjects receiving placebo, 1% for subjects receiving sofosbuvir + ribavirin for 12 weeks, <1% for subjects receiving sofosbuvir + ribavirin for 24 weeks, 11% for subjects receiving peginterferon alfa + ribavirin for 24 weeks and 2% for subjects receiving sofosbuvir + peginterferon alfa + ribavirin for 12 weeks.

Treatment-emergent adverse events observed in ≥15% of subjects in clinical trials are provided in below table. A side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

The most common adverse events (≥ 20%) for sofosbuvir + ribavirin combination therapy were fatigue and headache. The most common adverse events (≥ 20%) for sofosbuvir + peginterferon alfa + ribavirin combination therapy were fatigue, headache, nausea, insomnia and anemia.

Treatment-Emergent Adverse Events (All Grades) Reported in ≥ 15% of Subjects in Any Treatment Arm

	Interferon-free Regimens			Interferon-containing Regimens	
	PBO 12 weeks	Sofosbuvir + RBV[a] 12 weeks	Sofosbuvir + RBV[a] 24 weeks	Peg-IFN alfa + RBV[b] 24 weeks	Sofosbuvir + Peg-IFN alfa + RBV[a] 12 weeks
	N=71	N=650	N=250	N=243	N=327
Fatigue	24%	38%	30%	55%	59%
Headache	20%	24%	30%	44%	36%
Nausea	18%	22%	13%	29%	34%
Insomnia	4%	15%	16%	29%	25%
Pruritus	8%	11%	27%	17%	17%
Anemia	0%	10%	6%	12%	21%
Asthenia	3%	6%	21%	3%	5%
Rash	8%	8%	9%	18%	18%
Decreased Appetite	10%	6%	6%	18%	18%
Chills	1%	2%	2%	18%	17%
Influenza Like Illness	3%	3%	6%	18%	16%
Pyrexia	0%	4%	4%	14%	18%
Diarrhea	6%	9%	12%	17%	12%
Neutropenia	0%	<1%	<1%	12%	17%
Myalgia	0%	6%	9%	16%	14%
Irritability	1%	10%	10%	16%	13%

a Subjects received weight-based ribavirin (1000 mg per day if weighing < 75 kg or 1200 mg per day if weighing ≥ 75 kg).

b Subjects received 800 mg ribavirin per day regardless of weight.

With the exception of anemia and neutropenia, the majority of events presented in above table occurred at severity of grade 1 in sofosbuvir - containing regimens.

Less Common Adverse Reactions Reported in Clinical Trials (<1%): The following ADRs occurred in <1% of subjects receiving sofosbuvir in a combination regimen in any one trial. These events have been included because of their seriousness or assessment of potential causal relationship.

Hematologic Effects: pancytopenia (particularly in subjects receiving concomitant pegylated interferon).

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

Laboratory Abnormalities:

Changes in selected hematological parameters are described in below table. A side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

Percentage of Subjects Reporting Selected Hematological Parameters

	Interferon-free Regimens			Interferon-containing Regimens	
Hematological Parameters	PBO 12 weeks	Sofosbuvir + RBV[a] 12 weeks	Sofosbuvir + RBV[a] 24 weeks	Peg-IFN + RBV[b] 24 weeks	Sofosbuvir + Peg-IFN + RBV[a] 12 weeks
Hemoglobin (g/dL)	N=71	N=647	N=250	N=242	N=327
< 10	0	8%	6%	14%	23%
< 8.5	0	1%	<1%	2%	2%
Neutrophils (x10^9/L)					
≥0.5 -< 0.75	1%	<1%	0	12%	15%
< 0.5	0	<1%	0	2%	5%
Platelets (x10^9/L)					
≥25 - < 50	3%	<1%	1%	7%	<1%
< 25	0	0	0	0	0

Leaflet Size : 170 x 350 mm
Colour : Single Colour Black

a Subjects received weight-based ribavirin (1000 mg per day if weighing < 75 kg or 1200 mg per day if weighing ≥ 75 kg).

b Subjects received 800 mg ribavirin per day regardless of weight.

Bilirubin Elevations

Total bilirubin elevation of more than 2.5×ULN was observed in none of the subjects in the sofosbuvir + peginterferon alfa + ribavirin 12 weeks group and in 1%, 3% and 3% of subjects in the peginterferon alfa + ribavirin 24 weeks, sofosbuvir + ribavirin 12 weeks and sofosbuvir + ribavirin 24 weeks groups, respectively. Bilirubin levels peaked during the first 1 to 2 weeks of treatment and subsequently decreased and returned to baseline levels by post-treatment Week 4. These bilirubin elevations were not associated with transaminase elevations.

Creatine Kinase Elevations

Creatine kinase was assessed in the FISSION and NEUTRINO trials. Isolated, asymptomatic creatine kinase elevation of greater than or equal to 10×ULN was observed in <1%, 1% and 2% of subjects in the peginterferon alfa + ribavirin 24 weeks, sofosbuvir + peginterferon alfa + ribavirin 12 weeks and sofosbuvir + ribavirin 12 weeks groups, respectively.

Lipase Elevations

Isolated, asymptomatic lipase elevation of greater than 3×ULN was observed in <1%, 2%, 2%, and 2% of subjects in the sofosbuvir + peginterferon alfa + ribavirin 12 weeks, sofosbuvir + ribavirin 12 weeks, sofosbuvir + ribavirin 24 weeks and peginterferon alfa + ribavirin 24 weeks groups, respectively.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Sofosbuvir. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with Sofosbuvir in combination with another HCV direct acting antiviral.

OVERDOSE

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties:

Mechanism of Action

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

Pharmacodynamics

Effect on Electrocardiogram

The effect of sofosbuvir 400 and 1200 mg on QTc interval was evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects. At a dose three times the maximum recommended dose, sofosbuvir does not prolong QTc to any clinically relevant extent.

Pharmacokinetic Properties:

Absorption

The pharmacokinetic properties of sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Following oral administration of sofosbuvir, 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. Based on population pharmacokinetic analysis in subjects with genotype 1 to 6 HCV infection who were coadministered ribavirin (with or without pegylated interferon), geometric mean steady state AUC_{0-24} was 969 ng·hr/mL for sofosbuvir (N=838), and 6790 ng·hr/mL for GS-331007 (N=1695), respectively. Relative to healthy subjects administered sofosbuvir alone (N = 272), the sofosbuvir AUC_{0-24} was 60% higher; and GS-331007 AUC_{0-24} was 39% lower, respectively, in HCV-infected subjects. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg.

Effect of Food

Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardized high fat meal did not substantially affect the sofosbuvir C_{max} or AUC_{0-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 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, 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.

After a single 400 mg oral dose of [^{14}C]-sofosbuvir, sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

Elimination

Following a single 400 mg 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. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

Specific Populations

Race

Population pharmacokinetics analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

Gender

No clinically relevant pharmacokinetic differences have been observed between men and women for sofosbuvir and GS-331007.

Pediatric Patients

The pharmacokinetics of sofosbuvir in pediatric patients have not been established.

Geriatric Patients

Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (19 to 75 years) analyzed, age did not have a clinically relevant effect on the exposure to sofosbuvir and GS-331007.

Patients with Renal Impairment

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥ 50 and < 80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR <30 mL/min/1.73m^2) and subjects with end stage renal disease (ESRD) requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{0-inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir and GS-331007 AUC_{0-inf} was 28% and 1280% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after hemodialysis, respectively. A 4 hour hemodialysis session removed approximately 18% of administered dose. No dose adjustment 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 or ESRD. No dose recommendation can be given for patients with severe renal impairment or ESRD.

Patients with Hepatic Impairment

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on the exposure of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment.

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of sofosbuvir and GS-331007 are shown in below table.

Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir and GS331007 PK With/Without Coadministered Drug No Effect=1.00			
					C_{max}	AUC	C_{min}
Cyclosporine	600 single dose	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
				GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Darunavir (boosted with ritonavir)	800/100 once daily	400 single dose	18	sofosbuvir	1.45 (1.10, 1.92)	1.34 (1.12, 1.59)	NA
				GS-331007	0.97 (0.90, 1.05)	1.24 (1.18, 1.30)	NA
Efavirenz[c]	600 once daily	400 single dose	16	sofosbuvir	0.81 (0.60, 1.10)	0.94 (0.76, 1.16)	NA
Emtricitabine[c]	200 once daily			GS-331007	0.77 (0.70, 0.84)	0.84 (0.76, 0.92)	NA
Tenofovir disoproxil fumarate[c]	300 once daily						
Methadone	30 to 130 once daily	400 once daily	14	sofosbuvir	0.95[b] (0.68, 1.33)	1.30[b] (1.00, 1.69)	NA
				GS-331007	0.73[b] (0.65, 0.83)	1.04[b] (0.89, 1.22)	NA
Rilpivirine	25 once daily	400 single dose	17	sofosbuvir	1.21 (0.90, 1.62)	1.09 (0.94, 1.27)	NA
				GS-331007	1.06 (0.99, 1.14)	1.01 (0.97, 1.04)	NA
Tacrolimus	5 single dose	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
				GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA not available/not applicable

a All interaction studies conducted in healthy volunteers

b Administered as ATRIPLA

c Comparison based on historic control

No effect on the pharmacokinetic parameters of sofosbuvir and GS-331007 was observed with raltegravir.

The effects of sofosbuvir on the exposure of coadministered drugs are shown in below table.

Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir and GS331007 PK With/Without Coadministered Drug No Effect=1.00		
				C_{max}	AUC	C_{min}
Norelgestromin	norgestimate 0.18/0.215/0.25/ ethinyl estradiol 0.025 once daily	400 once daily	15	1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel				1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol				1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Raltegravir	400 twice daily	400 single dose	19	0.57 (0.44, 0.75)	0.73 (0.59, 0.91)	0.95 (0.81, 1.12)
Tacrolimus	5 single dose	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Tenofovir disoproxil fumarate[b]	300 once daily	400 single dose	16	1.25 (1.08, 1.45)	0.98 (0.91, 1.05)	0.99 (0.91, 1.07)

NA not available/not applicable

a All interaction studies conducted in healthy volunteers

b Administered as ATRIPLA

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with sofosbuvir: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, or rilpivirine.

Microbiology

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. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with IC_{50} 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.

Antiviral Activity

In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a, and chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a ranged from 0.014 to 0.11 µM. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.062 µM for genotype 1a (range 0.029-0.128 µM; N=67), 0.102 µM for genotype 1b (range 0.045-0.170 µM; N=29), 0.029 µM for genotype 2 (range 0.014-0.081 µM; N=15) and 0.081 µM for genotype 3a (range 0.024-0.181 µM; N=106). In infectious virus assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a were 0.03 and 0.02 µM, respectively. The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir. Evaluation of sofosbuvir in combination with interferon alpha or ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. An M289L substitution developed along with the S282T substitution in genotype 2a, 5 and 6 replicons. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In Clinical Trials

In a pooled analysis of 982 subjects who received Sofosbuvir in Phase 3 trials, 224 subjects had post-baseline NS5B genotypic data from next generation nucleotide sequencing (assay cutoff of 1%).

Treatment-emergent substitutions L159F (n= 6) and V321A (n= 5) were detected in post-baseline samples from GT3a-infected subjects across the Phase 3 trials. No detectable shift in the phenotypic susceptibility to sofosbuvir of subject isolates with L159F or V321A substitutions was seen. The sofosbuvir-associated resistance substitution S282T was not detected at baseline or in the failure isolates from Phase 3 trials. However, an S282T substitution was detected in one genotype 2b subject who relapsed at Week 4 post-treatment after 12 weeks of sofosbuvir monotherapy in the Phase 2 trial P7977-0523 [ELECTRON]. The isolate from this subject displayed a mean 13.5-fold reduced susceptibility to sofosbuvir. For this subject, the S282T substitution was no longer detectable at Week 12 post-treatment by next generation sequencing with an assay cut off of 1%.

In the trial done in subjects with hepatocellular carcinoma awaiting liver transplantation where subjects received up to 48 weeks of sofosbuvir and ribavirin, the L159F substitution emerged in multiple subjects with GT1a or GT2b HCV who experienced virologic failure (breakthrough and relapse). Furthermore, the presence of substitutions L159F and/or C316N at baseline was associated with sofosbuvir breakthrough and relapse post-transplant in multiple subjects infected with GT1b HCV. In addition, S282R and L320F substitutions were detected on-treatment by next generation sequencing in a subject infected with GT1a HCV with a partial treatment response.

The clinical significance of these substitutions is not known.

Cross Resistance

HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were susceptible to NS5A inhibitors and ribavirin. HCV replicons expressing the ribavirin-associated substitutions T390I and F415Y were susceptible to sofosbuvir. Sofosbuvir was active against HCV replicons with NS3/4A protease inhibitor, NS5B non-nucleoside inhibitor and NS5A inhibitor resistant variants.

HOW SUPPLIED

CAPRIBUVIR (Sofosbuvir Tablets 400 mg)

Orange, Oval, bevel biconvex, film-coated tablets de bossed with 'H' on one side and 'S14' on other side.

Container pack: HDPE Container with Child Resistant Plastic Caps with Pulp Liners x 28's (Box of 1's)

Storage Condition: Store at temperatures not exceeding 30°C.

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR REPORTING STATEMENT: For suspected adverse drug reaction. report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction.

Reference:

1. SOVALDI- sofosbuvir tablet, film coated USFDA Prescribing Information Leaflet

Capribuvir is manufactured under a license from **Gilead Sciences Ireland UC**

Manufactured by:

HETERO LABS LIMITED
Unit – V Sy. No.439, 440, 441 & 458,
TSIIC Formulation SEZ, Polepally village,
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Date of First Authorization/Renewal of the Authorization: March 2020

Date of Revision of Package Insert: