PRESCRIBING INFORMATION *To be sold by retail on the prescription of Hepatologist only*

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Sofosbuvir Tablets IP 400 mg

SOFOGEN-400

For India Only

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 Sofosbuvir Tablets 400 mg. 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.

1. Generic Name
Sofosbuvir Tablets IP 400 mg

2. Qualitative and Quantitative Composition
Each film-coated tablet contains:
Sofosbuvir IP 400 mg
Excipients q.s.
Colours: Titanium Dioxide IP and Sunset yellow FCF aluminum lake

3. DOSAGE FORM & STRENGTH
Film coated Tablet 400 mg for oral use

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Sofosbuvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

4.2 Posology and Method of 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.
Sofosbuvir treatment should be initiated and monitored by a physician experienced in the management of patients with chronic hepatitis C (CHC).
The recommended dose is one 400 mg tablet, taken orally, once daily with food.
Sofosbuvir should be used in combination with other medicinal products. Monotherapy of sofosbuvir is not recommended. The recommended co-administered medicinal product(s) and treatment duration for sofosbuvir combination therapy are provided in following table.

Table 1: Recommended co- administered medicinal product(s) and treatment duration for sofosbuvir combination therapy

Patient population*	Treatment	Duration
Patients with genotype 1, 4, 5 or 6 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks[a,b]
	Sofosbuvir + ribavirin Only for use in patients ineligible or intolerant to peginterferon alfa	24 weeks
Patients with genotype 2 CHC	Sofosbuvir + ribavirin	12 weeks[b]
Patients with genotype 3 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks[b]
	Sofosbuvir + ribavirin	24 weeks
Patients with CHC awaiting liver transplantation	Sofosbuvir + ribavirin	Until liver transplantation[c]

* Includes patients co-infected with human immunodeficiency virus (HIV).
a. For previously treated patients with HCV genotype 1 infection, no data exists with the combination of Sofosbuvir, ribavirin and peginterferon alfa.
b. Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy).
c. Patients awaiting liver transplantation below: The duration of administration of Sofosbuvir in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient.

The dose of ribavirin, when used in combination with Sofosbuvir is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg) and administered orally in two divided doses with food.

Dose modification
- Dose reduction of Sofosbuvir is not recommended.
- If sofosbuvir is used in combination with peginterferon alfa, and a patient has a serious adverse reaction potentially related to this drug, the peginterferon alfa dose should be reduced or discontinued.
- 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.

Following table provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 2: Ribavirin Dose Modification Guideline for Co-Administration with Sofosbuvir

Laboratory values	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Haemoglobin in subjects with no cardiac disease	<10 g/dL	<8.5 g/dL
Haemoglobin in subjects with history of stable cardiac disease	≥2 g/dL decrease in haemoglobin during any 4 week treatment period	<12 g/dL despite 4 weeks at reduced dose

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 (1,000 mg to 1,200 mg daily).

Discontinuation of dosing
If the other medicinal products used in combination with sofosbuvir are permanently discontinued, Sofosbuvir should also be discontinued.

Vomiting and missed doses
Patients should be instructed that if vomiting occurs within 2 hours of dosing an additional dose should be taken. If vomiting occurs more than 2 hours after dosing, no further dose is needed. These recommendations are based on the absorption kinetics of sofosbuvir and GS-331007 suggesting that the majority of the dose is absorbed within 2 hours after dosing.
If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the dose as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed not to take a double dose.

4.3 Contraindications
Sofosbuvir is contraindicated in
- Patients with hypersensitivity to sofosbuvir or to any other component of this formulation
- In 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 foetal death associated with ribavirin
- Medicinal products that are potent P-glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort). Co-administration will significantly decrease sofosbuvir plasma concentration and could result in loss of efficacy of sofosbuvir.

4.4 Special warnings and precautions for use
General
Sofosbuvir is not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection. If the other medicinal products used in combination with sofosbuvir are permanently discontinued, sofosbuvir should also be discontinued.

Severe bradycardia and heart block
Cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone with or without other medicinal products that lower heart rate. The mechanism is not established.
The concomitant use of amiodarone was limited through the clinical development of sofosbuvir. Cases are potentially life threatening, therefore amiodarone should only be used in patients on sofosbuvir when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.
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.
Should concomitant use of amiodarone be considered necessary it is recommended that patients are closely monitored when initiating sofosbuvir. Patients who are identified as being high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.
Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir.
All patients receiving sofosbuvir in combination amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.
Treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection
Sofosbuvir has not been studied in a phase III study in treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infections. Thus, the optimal treatment duration in this population has not been established. Consideration should be given to patients, with potentially extending the duration of therapy with sofosbuvir, peginterferon alfa and ribavirin beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon- based therapies (advanced fibrosis/cirrhosis, high baseline viral concentrations, black race and IL28B non CC genotype).

Treatment of patients with genotype 5 or 6 HCV infection
The clinical data to support the use of sofosbuvir in patients with genotype 5 and 6 HCV infection is very limited.

Interferon-free therapy for genotype 1, 4, 5 and 6 HCV infection
Interferon-free regimens for patients with genotype 1, 4, 5 and 6 HCV infections with sofosbuvir have not been investigated in Phase III studies. The optimal regimen and treatment duration have not been established. Such regimens should only be used for patients that are intolerant to or ineligible for interferon therapy and are in urgent need of treatment.

Co-administration with other direct-acting antivirals against HCV
Sofosbuvir should only be co-administered with other direct-acting antiviral medicinal products if the benefit is considered to outweigh the risks based upon available data. There are no data to support the co-administration of sofosbuvir and telaprevir or boceprevir. Such co-administration is not recommended.

Pregnancy and concomitant use with ribavirin
When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during the treatment and for a period of time after the treatment.

Use with moderate P-gp inducers
Medicinal products that are moderate P-glycoprotein (P-gp) inducers in the intestine (e.g. Oxcarbazepine and modafinil) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir. Co-administration of such medicinal products is not recommended with sofosbuvir.

Use in diabetic patients
Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated.

Renal impairment
The safety of sofosbuvir has not been assessed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m2) or ESRD requiring haemodialysis. Furthermore, the appropriate dose has not been established. When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin.

HCV/HBV (hepatitis B virus) co-infection
Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

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

4.5 Drug Interactions
Sofosbuvir is a nucleotide prodrug. After oral administration, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic and intestinal metabolism. Intracellular hydrolytic prodrug cleavage catalyzed by enzymes including carboxylesterase 1 and sequential phosphorylation steps catalyzed by nucleotide kinases result in formation of the pharmacologically active uridine nucleoside analogue triphosphate. The predominant inactive circulating metabolite GS-331007 that accounts for greater than 90% of drug-related material systemic exposure is formed through pathways sequential and parallel to formation of active metabolite. The parent sofosbuvir accounts for approximately 4% of drug-related material systemic exposure.

Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP). Medicinal products that are potent P-gp inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir and contraindicated with sofosbuvir.

Co-administration of sofosbuvir with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus sofosbuvir may be co-administered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of medicinal products that are substrates of these transporters.

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 medicinal products.
The following table summarizes Drug interaction information for sofosbuvir with potential concomitant medicinal products (where 90% confidence interval (CI) of the geometric least-squares mean (GLSM) ratio were within "↔", extended above " ↑ ", or extended below " ↓ " the predetermined equivalence boundaries).

Table 3: Interactions between sofosbuvir and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]	Recommendation concerning co-administration with Sofosbuvir
ANALEPTICS		
Modafinil	Interaction not studied. *Expected:* ↓ Sofosbuvir ↓ GS-331007	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.
ANTIARRHYTHMICS		
Amiodarone	Interaction not studied.	Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with sofosbuvir.
ANTICOAGULANTS		
Vitamin K antagonists	Interaction not studied.	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with sofosbuvir.
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Interaction not studied. Expected: ↓ Sofosbuvir ↔ GS-33100	Sofosbuvir is contraindicated with carbamazepine, phenobarbital and phenytoin, potent intestinal P-gp inducers.
Oxcarbazepine	Interaction not studied Expected: ↓ Sofosbuvir ↓ GS-331007	Co-administration of Sofosbuvir with oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir. Such co-administration is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin (600 mg single dose)	Sofosbuvir ↓ C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) C_{min} (NA) GS-331007 ↔ C_{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) C_{min} (NA)	Sofosbuvir is contraindicated with rifampicin, a potent intestinal P-gp inducer
Rifabutin Rifapentine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir is contraindicated with rifabutin, a potent intestinal P-gp inducer. Co-administration of sofosbuvir with rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir. Such co-administration is not recommended.
HERBAL SUPPLEMENTS		
St. John's wort *(Hypericum perforatum)*	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir should not be used with St. John's wort, a potent intestinal P-gp inducer.
HCV ANITIVIRAL AGENTS: HCV PROTEASE INHIBITORS		
Boceprevir (BOC) Telaprevir (TPV)	Interaction not studied. *Expected:* ↑ Sofosbuvir (TPV) ↔ Sofosbuvir (BOC) ↔ GS-331007 (TPV or BOC)	No drug-drug interactio data exists regarding the co- administration of sofosbuvir with boceprevir or telaprevir.
NARCOTIC ANALGESICS		
Methadone[f] (Methadone maintenance therapy [30 to 130 mg/daily])	*R-methadone* ↔ C_{max} 0.99 (0.85, 1.16) ↔AUC 1.01 (0.85, 1.21) ↔C_{min} 0.94 (0.77, 1.14) *S-methadone* ↔ C_{max} 0.95 (0.79, 1.13) ↔ AUC 0.95 (0.77, 1.17) ↔ C_{min} 0.95 (0.74, 1.22) *Sofosbuvir* ↓ C_{max} 0.95c (0.68, 1.33) ↑ AUC 1.30c (1.00, 1.69) C_{min} (NA) *GS-331007* ↓ C_{max} 0.73c (0.65, 0.83) ↔ AUC 1.04c (0.89, 1.22) C_{min} (NA))	No dose adjustment of sofosbuvir or methadone is required when sofosbuvir and methadone are used concomitantly.
IMMUNOSUPPRESSANTS		
Ciclosporin[e] (600 mg single dose)	*Ciclosporin* ↔ C_{max} 1.06 (0.94, 1.18) ↔ AUC 0.98 (0.85, 1.14) C_{min} (NA) *Sofosbuvir* ↑ C_{max} 2.54 (1.87, 3.45) ↑ AUC 4.53 (3.26, 6.30) C_{min} (NA) *GS-331007* ↓ C_{max} 0.60 (0.53, 0.69) ↔ AUC 1.04 (0.90, 1.20)	No dose adjustment of sofosbuvir or ciclosporin is required when sofosbuvir and ciclosporin are used
Tacrolimus[e] (5 mg single dose)	*Tacrolimus* ↓ C_{max} 0.73 (0.59, 0.90) ↔ AUC 1.09 (0.84, 1.40) C_{min} (NA) *Sofosbuvir* ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) C_{min} (NA) *GS-331007* ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13) C_{min} (NA)	No dose adjustment of sofosbuvir or tacrolimus is required when sofosbuvir and tacrolimus are used concomitantly.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz[f] (600 mg once daily)[d]	*Efavirenz* ↔ C_{max} 0.95 (0.85, 1.06) ↔ AUC 0.96 (0.91, 1.03) ↔ C_{min} 0.96 (0.93, 0.98) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or efavirenz is required when sofosbuvir and efavirenz are used concomitantly.
Emtricitabine[f] (200 mg once daily)[d]	*Emtricitabine* ↔ C_{max} 0.97 (0.88, 1.07) ↔ AUC 0.99 (0.94, 1.05) ↔ C_{min} 1.04 (0.98, 1.11) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) GS-331007 ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or emtricitabine is required when sofosbuvir and emtricitabine are used concomitantly.
Tenofovir disoproxil[f] (245 mg once daily)[d]	*Tenofovir* ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or tenofovir disoproxil is required when sofosbuvir and tenofovir disoproxil are used concomitantly
Rilpivirine[f] (25 mg once daily)	*Rilpivirine* ↔ C_{max} 1.05 (0.97, 1.15) ↔ AUC 1.06 (1.02, 1.09) ↔ C_{min} 0.99 (0.94, 1.04) *Sofosbuvir* ↑ C_{max} 1.21 (0.90, 1.62) ↔ AUC 1.09 (0.94, 1.27) C_{min} (NA) *GS-331007* ↔ C_{max} 1.06 (0.99, 1.14) ↔ AUC 1.01 (0.97, 1.04) C_{min} (NA)	No dose adjustment of sofosbuvir or rilpivirine is required when sofosbuvir and rilpivirine are used concomitantly.
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Darunavir boosted with ritonavir[f] (800/100 mg once daily)	*Darunavir* ↔ C_{max} 0.97 (0.94, 1.01) ↔ AUC 0.97 (0.94, 1.00) ↔ C_{min} 0.86 (0.78, 0.96) *Sofosbuvir* ↑ C_{max} 1.45 (1.10, 1.92) ↑ AUC 1.34 (1.12, 1.59) C_{min} (NA) *GS-331007* ↔ C_{max} 0.97 (0.90, 1.05) ↔ AUC 1.24 (1.18, 1.30) C_{min} (NA)	No dose adjustment of sofosbuvir or darunavir (ritonavir boosted) is required when sofosbuvir and darunavir are used concomitantly.
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		
Raltegravir[f] (400 mg twice daily)	*Raltegravir* ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{min} 0.95 (0.81, 1.12) *Sofosbuvir* ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) C_{min} (NA) *GS-331007* ↔ C_{max} 1.09 (0.99, 1.20) ↔ AUC 1.03 (0.97, 1.08) C_{min} (NA)	No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly.

380 mm

200 mm

Spec.: 41 ± 15% Gsm Bible Paper
Dimension: 200x380 mm
Folding Size: 50x47.5 mm
Reason for change: New Brand

ORAL CONTRACEPTIVES		
Norgestimate/ethinyl estradiol	Norgestromin ↔ C^{max} 1.06 (0.93, 1.22) ↔ AUC 1.05 (0.92, 1.20) C_{min} (NA) Norgestrel ↔ C_{max} 1.18 (0.99, 1.41) ↔ AUC 1.19 (0.98, 1.44) C_{min} (NA) Ethinyl estradiol ↔ C_{max} 1.14 (0.96, 1.36) ↔ AUC 1.08 (0.93, 1.25) C_{min} (NA)	No dose adjustment of norgestimate/ethinyl estradiol is required when sofosbuvir and norgestimate/ethinyl estradiol are used concomitantly.

NA = not available/not applicable

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics with/without sofosbuvir and mean ratio of sofosbuvir and GS-331007 with/without co-administered drug. No effect = 1.00
b. All interaction studies conducted in healthy volunteers
c. Comparison based on historical control
d. Administered as Atripla
e. Bioequivalence boundary 80%-125%
f. Equivalence boundary 70%-143

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy:

Risk Summary

If Sofosbuvir is administered with ribavirin or peginterferon alfa and ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin and/or peginterferon alfa prescribing information for more information on ribavirin- and peginterferon alfa-associated risks of use during pregnancy.

No adequate human data are available to establish whether or not sofosbuvir poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with sofosbuvir at exposures greater than those in humans at the recommended human dose (RHD). During organogenesis in the rat and rabbit, systemic exposures (AUC) to the predominant circulating metabolite of sofosbuvir (GS-331007) were ≥ 5 (rats) and 12 (rabbits) times the exposure in humans at the RHD. In the rat pre/postnatal development study, maternal systemic exposure (AUC) to GS-331007 was ≥6 times the exposure in humans at the RHD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Animal Data

Sofosbuvir was administered orally to pregnant rats (up to 500 mg/kg/day) and rabbits (up to 300 mg/kg/day) on gestation days 6 to 18 and 6 to 19, respectively, and also to rats (oral doses up to 500 mg/kg/day) on gestation day 6 to lactation/post-partum day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. Systemic exposures (AUC) to the predominant circulating metabolite of sofosbuvir (GS-331007) were ≥ 5 (rats) and 12 (rabbits) times the exposure in humans at the RHD, with exposures increasing during gestation from approximately 5 to 10 (rats) and 12 to 28 (rabbits) times the exposure in humans at the RHD.

Nursing mothers

It is not known whether sofosbuvir and its metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats, without effect on nursing pups. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sofosbuvir and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

If sofosbuvir is administered in a regimen containing ribavirin, the information for ribavirin with regard to nursing mothers also applies to this combination regimen.

Pediatrics Use

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

Geriatrics Use

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 appropriate dose of sofosbuvir have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m2) or end stage renal disease (ESRD) requiring haemodialysis.

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). The safety and efficacy of sofosbuvir have not been established in patients with decompensated cirrhosis.

4.7 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.

4.8 Undesirable Effects

During treatment with sofosbuvir in combination with ribavirin or with peginterferon alfa and ribavirin, the most frequently reported adverse drug reactions were consistent with the expected safety profile of ribavirin and peginterferon alfa treatment, without increasing the frequency or severity of the expected adverse drug reactions.

Sofosbuvir has mainly been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse drug reactions occurring in patients receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

The following adverse drug reactions have been identified with sofosbuvir in combination with ribavirin or in combination with peginterferon alfa and ribavirin (Table 4). The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000).

Table 4: Adverse Drug Reactions Identified With Sofosbuvir in Combination with Ribavirin or Peginterferon Alfa and Ribavirin

Frequency	SOF[a] + RBV[b]	SOF + PEG[c] + RBV
Infections and infestations		
Common	Nasopharyngitis	
Blood and lymphatic system disorders:		
Very common	Haemoglobin decreased	Anaemia, neutropenia, lymphocyte count decreased, platelet count decreased
Common	Anaemia	
Metabolism and nutrition disorders:		
Very common		Decreased appetite
Common		Weight decreased
Psychiatric disorders:		
Very common	Insomnia	Insomnia
Common	Depression	Depression, anxiety, agitation
Nervous system disorders:		
Very common	Headache	Dizziness, headache
Common	Disturbance in attention	Migraine, memory impairment, disturbance in attention
Eye disorders:		
Common		Vision blurred
Respiratory, thoracic and mediastinal disorders:		
Very common		dyspnoea, cough
Common	Dyspnoea, dyspnoea exertional, cough	dyspnoea exertional
Gastrointestinal disorders:		
Very common	nausea	diarrhoea, nausea, vomiting
Common	abdominal discomfort, constipation, dyspepsia	constipation, dry mouth, gastroesophageal reflux
Hepatobiliary disorders:		
Very common	blood bilirubin increased	blood bilirubin increased
Skin and subcutaneous tissue disorders:		
Very common		rash, pruritus
Common	alopecia, dry skin, pruritus	alopecia, dry skin
Musculoskeletal and connective tissue disorders:		
Very common		arthralgia, myalgia
Common	arthralgia, back pain, muscle spasms, myalgia	back pain, muscle spasms
General disorders and administration site conditions:		
Very common	fatigue, irritability	chills, fatigue, influenza-like illness, irritability, pain, pyrexia
Common	pyrexia, asthenia	chest pain, asthenia

a. SOF = sofosbuvir; b. RBV = ribavirin; c. PEG =peginterferon alfa.

The following are the adverse reactions occurred in less than 1% of subjects receiving Sofosbuvir in a combination regimen. 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.

Table 5: Percentage of subjects reporting selected hematological parameters

Hematological Parameters	Interferon-free Regimens			Interferon-containing Regimens	
	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)					
<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					
≥25 – <50	3%	<1%	1%	7%	<1%
<25	0	0	0	0	0

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 2.5xULN was observed in none of the subjects in the sofosbuvir + peginterferon alfa + ribavirin 12 weeks group and observed in the peginterferon alfa + ribavirin 24 weeks, sofosbuvir + ribavirin 12 weeks and sofosbuvir+ ribavirin 24 weeks treatment, 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

Isolated, asymptomatic creatine kinase elevation of greater than or equal to 10xULN was observed in the peginterferon alfa + ribavirin 24 weeks, sofosbuvir + peginterferon alfa + ribavirin 12 weeks and sofosbuvir + ribavirin 12 weeks treatments, respectively.

Lipase elevations

Isolated, asymptomatic lipase elevation of greater than 3xULN was observed in the sofosbuvir + peginterferon alfa + ribavirin 12 weeks, sofosbuvir + ribavirin 12 weeks, sofosbuvir + ribavirin 24 weeks and peginterferon alfa + ribavirin 24 weeks treatments, respectively.

Patients with HCV/HIV 1 Co-infection

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 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.

Post marketing experience

The following adverse reactions have been identified during post approval use of sofosbuvir.

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.

Skin and Subcutaneous Tissue Disorders: Skin rashes, sometimes with blisters or angioedema-like swelling, Angioedema

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form **(form.heteroworld.com)** or by **Hetero Helpline No.180-020-01303** and for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com.

4.9 Overdose

The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1,200 mg administered to 59 healthy subjects. In that study, there were no untoward effects observed at this dose level, and adverse reactions were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups. The effects of higher doses are unknown.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Sofosbuvir 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. GS-461203 (the active metabolite of sofosbuvir) is not an inhibitor of human DNA and RNA polymerases or an inhibitor of mitochondrial RNA polymerase.

5.2 Pharmacodynamic properties

Antiviral activity

In HCV replicon assays, the effective concentration (EC_{50}) values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a were 0.04, 0.11, 0.05, 0.05 and 0.04 µM, respectively, and EC_{50} values of sofosbuvir against chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a were 0.014 to 0.015 µM. The mean ± SD EC_{50} of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.068 ± 0.024 µM for genotype 1a (n = 67), 0.11 ± 0.029 µM for genotype 1b (n = 29), 0.035 ± 0.018 µM for genotype 2 (n = 15) and 0.085 ± 0.034 µM for genotype 3a (n = 106). In these assays, the *in vitro* antiviral activity of sofosbuvir against the less common genotypes 4, 5 and 6 was similar to that observed for genotypes 1, 2 and 3.

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

Resistance

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. 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.

Cross resistance

HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were fully susceptible to other classes of anti-HCV agents. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors and it was fully active against substitutions associated with resistance to other direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors, NS3 protease inhibitors and NS5A inhibitors.

5.3 Pharmacokinetic properties

Absorption

Following oral administration, sofosbuvir was absorbed quickly and the peak plasma concentration was 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 standardized high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold, with little effect on peak concentration. The exposure to GS-331007 was not altered in the presence of a high-fat meal.

Distribution

Sofosbuvir is not a substrate for hepatic transporters including the organic anion-transporting polypeptide (OATP) 1B1 or 1B3. GS-331007 is not a substrate or inhibitor for renal transporters including organic anion transporter (OAT) 1 or 3, or organic cation transporter (OCT) 2, MRP2, P-gp, BCRP or MATE1 when subject to active tubular secretion.

Sofosbuvir is approximately 85% bound to human plasma proteins (ex vivo data) and the binding is independent of drug concentration over the range of 1 µg/mL to 20µg/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 metabolised 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. Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes.

After a single 400 mg oral dose of [14C]-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.

Excretion

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, faeces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This data indicate that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. The median terminal half-lives of sofosbuvir and GS- 331007 were 0.4 and 27 hours respectively.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

In repeat dose toxicology studies in rat and dog, high doses of the 1:1 diastereomeric mixture caused adverse liver (dog) and heart (rat) effects and gastrointestinal reactions (dog). Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity; however, exposure to the major metabolite GS-331007 at the adverse dose was 29 times (rat) and 123 times (dog) higher than the clinical exposure at 400 mg sofosbuvir. No liver or heart findings were observed in chronic toxicity studies at exposures 9 times (rat) and 27 times (dog) higher than the clinical exposure.

Sofosbuvir was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo mouse micronucleus assays.

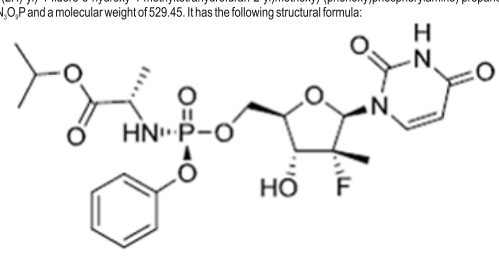
Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was up to 30 times (mouse) and 15 times (rat) higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir had no effects on embryo-foetal viability or on fertility in rat and was not teratogenic in rat and rabbit development studies. No adverse effects on behaviour, reproduction or development of offspring in rat were reported. In rabbit studies exposure to sofosbuvir was 9 times the expected clinical exposure. In the rat studies, exposure to sofosbuvir could not be determined but exposure margins based on the major human metabolite ranged from 8 to 28 times higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir-derived material was transferred through the placenta in pregnant rats and into the milk of lactating rats.

7. Description

Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase with the IUPAC name (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:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Refer on Pack

8.3 Packing Information

Each HDPE container: 28's pack

8.4 Storage and handling instructions

Store protected from moisture at a temperature not exceeding 30°C.

Keep container tightly closed.
Keep out of reach of children.
Dispense in original container.
Do not use if seal over bottle opening is broken or missing.

9. PATIENT COUNSELLING INFORMATION

Risk of Hepatitis B Virus Reactivation in Patients Co-infected with HCV and HBV

Inform patients that HBV reactivation can occur in patients co-infected with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of HBV infection.

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Advise patients to seek medical evaluation immediately for symptoms of bradycardia such as near-fainting or fainting, dizziness or light headedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion or memory problems.

Pregnancy

Advise patients to avoid pregnancy during combination treatment with Sofosbuvir and ribavirin or Sofosbuvir and peginterferon and ribavirin. Inform patients to notify their health care provider immediately in the event of a pregnancy.

Drug Interactions

Advise patients that Sofosbuvir may interact with some drugs; therefore, patients should be advised to report the use of any prescription, non-prescription medication or herbal products to their healthcare provider.

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment or in the event of treatment failure should be taken.

Important Information on Coadministration with Ribavirin or Peginterferon and Ribavirin

Advise patients that the recommended regimen for patients with genotype 1 or 4 HCV infection is Sofosbuvir administered in combination with peginterferon alfa and ribavirin and the recommended regimen for patients with genotype 2 or 3 HCV infection is Sofosbuvir administered in combination with ribavirin. If peginterferon and/or ribavirin are permanently discontinued, Sofosbuvir should also be discontinued.

10. DETAILS OF MANUFACTURER

Hetero Labs Limited (Unit-II),
Village: Kalyanpur, Chakkan Road,
Tehsil: Baddi, Distt: Solan,
Himachal Pradesh-173205, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

MF-72/2015, 12 Mar 2015

12. DATE OF REVISION

06-12-2022

SOFOGEN-400 is manufactured under license from Gilead Sciences Ireland UC.

For use in India only; Not for export.

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GENYGI

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Genygi Life Sciences Private Limited
SS - 29, Second Floor, Aditya Mega Mall,
Plot # 9D, Delhi - 110032

380 mm

200 mm

Spec.: 41 ± 15% Gsm Bible Paper
Dimension: 200x380 mm
Folding Size: 50x47.5 mm
Reason for change: New Brand