

## HEPSITAJ Tablets (Sofosbuvir )



### Composition

#### HEPSITAJ Tablets

Each film-coated tablet contains:

Sofosbuvir ..... 400 mg

**Colours:** Red Oxide of Iron & Titanium Dioxide USP

#### HEPSITAJ- A.T\* Tablets

Each tablet contains:

Ledipasvir ..... 90 mg

Sofosbuvir ..... 400 mg

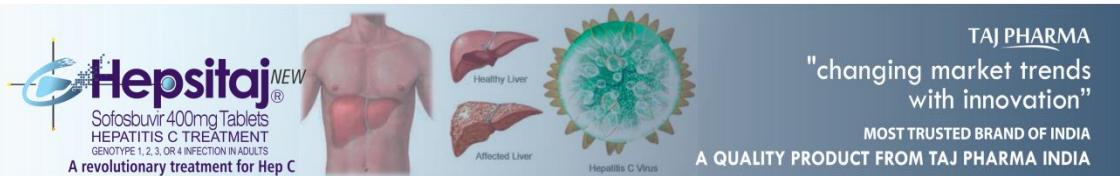
Excipients.....q.s.

**Colours:** Ferric Oxide USP-NF Red, Ferric Oxide USP-NF Yellow & Titanium Dioxide USP.

\*ADVANCE TREATMENTS.

### Dosage Form

Tablet



### Pharmacology

#### Pharmacodynamics

##### **Mechanism of Action**

Sofosbuvir is a direct-acting antiviral (DAA) agent against the hepatitis C virus (HCV). It 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 a pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator.

##### **Effect on Electrocardiogram**

The effect of sofosbuvir 400 and 1,200 mg on the QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) four-period crossover through a 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.

## **Pharmacokinetics**

### ***Absorption***

The pharmacokinetic properties of sofosbuvir and its predominant circulating metabolite (GS-331007) have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Following oral administration, sofosbuvir was absorbed with a peak plasma concentration observed at ~0.5–2 hours post-dose, regardless of dose level. Peak plasma concentration of the metabolite was observed between 2 and 4 hours post-dose. Based on population pharmacokinetic analysis in subjects with genotype 1–6 HCV infection who were co-administered ribavirin (with or without pegylated interferon), the geometric mean, steady-state AUC<sub>0–24</sub> of sofosbuvir (N=838) and GS-331007 (N=1,695) were 828 ng·hr/mL and 6,790 ng·hr/mL, respectively. Relative to healthy subjects administered sofosbuvir alone (N = 272), the sofosbuvir AUC<sub>0–24</sub> was 39% higher and, GS-331007 AUC<sub>0–24</sub> 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 1,200 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<sub>max</sub> or AUC<sub>0–inf</sub>. 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 the sofosbuvir metabolite was minimal in human plasma. After a single 400 mg dose of -sofosbuvir in healthy subjects, the blood to plasma ratio of <sup>14</sup>C-radioactivity was approximately 0.7.

### ***Metabolism***

Sofosbuvir is extensively metabolized in the liver to form a 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) is followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of a nucleoside metabolite, GS-331007, that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

After a single 400 mg oral dose of -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 -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 the metabolite. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

### ***Special Populations***

#### ***Gender***

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

#### ***Race***

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

#### Geriatic

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 .

#### Pediatric

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

#### Renal Impairment

The pharmacokinetics of sofosbuvir were studied in HCV-negative subjects with mild (eGFR  $\geq 50$  and  $< 80$  mL/min/1.73m<sup>2</sup>), moderate (eGFR  $\geq 30$  and  $< 50$  mL/ min/ 1.73 m<sup>2</sup>), severe renal impairment (eGFR  $< 30$  mL/min/1.73m<sup>2</sup>) 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<sup>2</sup>), the sofosbuvir AUC<sub>0-inf</sub> was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC<sub>0-inf</sub> was 55%, 88% and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir and GS-331007 AUC<sub>0-inf</sub> was 28% and 1,280% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2,070% higher when sofosbuvir was dosed 1 hour after hemodialysis, respectively. A 4-hour hemodialysis session removed approximately 18% of the administered dose. No dose adjustment is required for patients with mild or moderate renal impairment. The safety and efficacy of sofosbuvir has 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 .

#### Hepatic Impairment

The pharmacokinetics of sofosbuvir was studied following a 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<sub>0-24</sub> were 126% and 143% higher in moderate and severe hepatic impairment while the GS-331007 AUC<sub>0-24</sub> 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 .

### **Indications**

**HEPSITAJ Tablets**, which contain sofosbuvir, a HCV nucleotide analog NS5B polymerase inhibitor, are indicated in combination with under medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

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 **HEPSITAJ Tablets**:

- 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 .

### **Dosage and Administration**

The recommended dose of **HEPSITAJ Tablets** 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 (peg)-interferon alfa and ribavirin for the treatment of CHC in adults. The recommended regimen and treatment duration for sofosbuvir combination therapy is provided in Table 1.

**Table 1: Recommended regimens and treatment duration for sofosbuvir combination therapy in HCV mono-infected and HCV/HIV-1 co-infected patients**

	Treatment	Duration
Patients with genotype 1 or 4 CHC	Sofosbuvir + peg-interferon alfa <sup>a</sup> + ribavirin <sup>b</sup>	12 weeks
Patients with genotype 2 CHC	Sofosbuvir + ribavirin <sup>b</sup>	12 weeks
Patients with genotype 3 CHC	Sofosbuvir + ribavirin <sup>b</sup>	24 weeks

<sup>a</sup> See peg-interferon alfa prescribing information for dosing recommendation for patients with genotype 1 or 4 CHC.

<sup>b</sup> Dose of ribavirin is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 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.

#### ***Genotypes 1 and 4***

If a patient has a serious adverse reaction potentially related to peg-interferon alfa and/or ribavirin, the peg-interferon alfa and/or ribavirin dose should be reduced or discontinued. Refer to the peg-interferon alfa and ribavirin prescribing information for additional information about how to reduce and/or discontinue the peg-interferon alfa and/or ribavirin dose.

#### ***Genotypes 2 and 3***

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

**Table 2: Ribavirin dose modification guideline for co-administration with sofosbuvir**

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day <sup>a</sup> if:	Discontinue Ribavirin if: <sup>b</sup>

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

<sup>a</sup> The daily dose of ribavirin is administered orally in two divided doses with food.

<sup>b</sup> 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 agents used in combination with sofosbuvir are permanently discontinued, sofosbuvir should also be discontinued.

## Severe Renal Impairment and ESRD

No dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup>) or with ESRD due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite .

## Contraindications

When sofosbuvir is used in combination with ribavirin or peg-interferon alfa/ribavirin, the contraindications applicable to those agents are applicable to combination therapies. Refer to the prescribing information of peg-interferon alfa and ribavirin for a list of their contraindications.

## Warnings and Precautions

### Drug Interactions

#### Potential for Drug Interactions

After oral administration of sofosbuvir, it is rapidly converted to the predominant circulating metabolite, GS-331007, that accounts for greater than 90% of drug related material systemic exposure, whereas 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 the drug transporter, P-gp, and the 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 concentrations, leading to a reduced therapeutic effect of sofosbuvir and, thus, should not be used with sofosbuvir . Co-administration of sofosbuvir with drugs that inhibit P-gp and/or BCRP may increase the sofosbuvir plasma concentration without increasing the GS-331007 plasma concentration; accordingly, 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 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 Table 3. The drug interactions described are based on potential drug interactions that may occur with sofosbuvir. The table is not all-inclusive.

**Table 3: Potentially significant drug interactions: Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction<sup>a</sup>**

Concomitant Drug Class: Drug Name	Effect on Concentration <sup>b</sup>	Clinical Comment
<b>Anti-arrhythmics:</b> Amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown	Co-administration of amiodarone with sofosbuvir in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Co-administration of amiodarone with sofosbuvir in combination with another DAA is not recommended; if co-administration is required, cardiac monitoring is recommended
<b>Anticonvulsants:</b> Carbamazepine Phenytoin Oxcarbazepine	Phenobarbital  ↓ sofosbuvir ↓ GS-331007	Co-administration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Co-administration is not recommended.
<b>Antimycobacterials:</b> Rifabutin Rifampin Rifapentine	  ↓ sofosbuvir ↓ GS-331007	Co-administration of sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Co-administration

		is not recommended. Sofosbuvir should not be used with rifampin, a potent intestinal P-gp inducer.
<b>Herbal Supplements:</b> St. John's Wort ( <i>Hypericum perforatum</i> )	↓ sofosbuvir ↓ GS-331007	Sofosbuvir should not be used with St. John's Wort, a potent intestinal P-gp inducer.
<b>HIV Protease Inhibitors:</b> Tipranavir/ritonavir	↓ sofosbuvir ↓ GS-331007	Co-administration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Co-administration is not recommended.

<sup>a</sup> This table is not all-inclusive.

<sup>b</sup> ↓ = decrease.

#### **Drugs without Clinically Significant Interactions with Sofosbuvir**

In addition to the drugs included in Table 3, 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, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

#### **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.

#### **Serious Symptomatic Bradycardia When Co-administered with Amiodarone and another HCV DAA**

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is co-administered 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 (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 co-administration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Co-administration of amiodarone with sofosbuvir in combination with another DAA is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be co-administered 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 co-administration 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 .

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

Drugs that are P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir. The use of rifampin and St. John's wort with sofosbuvir is not recommended .

#### **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.

#### **Related Products Not Recommended**

The use of **HEPSITAJ** with other products containing sofosbuvir is not recommended.

### **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 less than the lower limit of quantification (LLOQ) at 12 weeks post-transplant. HCV-infected subjects, regardless of genotype, with hepatocellular carcinoma 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 1,000–1,200 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 less than the LLOQ at the time of transplantation. Of the 37 subjects, the post-transplant virologic response (pTVR) rate was 64% (23/36) in the 36 evaluable subjects who had 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 has 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.

## **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/1.73 m<sup>2</sup>) or ESRD requiring hemodialysis. No dose recommendation can be given for patients with severe renal impairment or ESRD . Refer also to ribavirin and peg-interferon 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 peg-interferon alfa prescribing information for contraindication in hepatic decompensation.

## **Pregnancy**

### ***Pregnancy Category X: Use with Ribavirin or Peg-interferon 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 peg-interferon 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. There are no data on the effectiveness of systemic hormonal contraceptives in women taking sofosbuvir; therefore, two non-hormonal methods of contraception should be used during treatment with sofosbuvir and concomitant ribavirin .

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.

## **Lactation**

It is not known whether sofosbuvir and its metabolite(s) 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 the 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. Also see 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 years 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 .

## Undesirable Effects

### Clinical Trials Experience

Sofosbuvir should be administered with ribavirin or peg-interferon alfa/ribavirin. Refer to the prescribing information of peg-interferon 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 the sofosbuvir + ribavirin 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 + peg-interferon alfa + ribavirin combination therapy for 12 weeks, 243 subjects who received peg-interferon alfa + ribavirin for 24 weeks, and 71 subjects who received placebo 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 peg-interferon alfa + ribavirin for 24 weeks, and 2% for subjects receiving sofosbuvir + peg-interferon alfa + ribavirin for 12 weeks.

Treatment-emergent adverse events observed in ≥15% of subjects in clinical trials are provided in Table 4. 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 the sofosbuvir + ribavirin combination therapy were fatigue and headache. The most common adverse events (≥20%) for the sofosbuvir + peg-interferon alfa + ribavirin combination therapy were fatigue, headache, nausea, insomnia and anemia.

**Table 4: 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 <sup>a</sup> 12 weeks	Sofosbuvir RBV <sup>a</sup> 24 weeks	Peg-IFN alfa + RBV <sup>b</sup> 24 weeks	Sofosbuvir + Peg-IFN alfa + RBV <sup>a</sup> 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%

Peg-IFN=peg-interferon; RBV=ribavirin; PBO=placebo

<sup>a</sup> Subjects received weight-based ribavirin (1,000 mg per day if weighing <75 kg or 1,200 mg per day if weighing ≥75 kg).

<sup>b</sup> Subjects received 800 mg ribavirin per day regardless of weight.

With the exception of anemia and neutropenia, the majority of events presented in Table 4 occurred at severity of grade 1 in sofosbuvir-containing regimens.

#### ***Less Common Adverse Reactions Reported in Clinical Trials (<1%):***

The following adverse events 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 peg-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 Table 5. A side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

**Table 5: Percentage of subjects reporting selected hematological parameters**

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

Peg-IFN=peg-interferon; RBV=ribavirin; PBO=placebo

<sup>a</sup> Subjects received weight-based ribavirin (1,000 mg per day if weighing <75 kg or 1,200 mg per day if weighing ≥75 kg).

<sup>b</sup> 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 12 week sofosbuvir + peg-interferon alfa + ribavirin group and in 1%, 3% and 3% of subjects in the 24 weeks' peg-interferon alfa + ribavirin, 12 weeks' sofosbuvir + ribavirin and sofosbuvir + ribavirin 24 weeks' groups, respectively. Bilirubin levels peaked during the first 1–2 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 peg-interferon alfa + ribavirin 24 weeks', sofosbuvir + peg-interferon 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 + peg-interferon alfa + ribavirin 12 weeks', sofosbuvir + ribavirin 12 weeks', sofosbuvir + ribavirin 24 weeks' and peg-interferon alfa + ribavirin 24 weeks' groups, respectively.

### **Patients with HCV/HIV-1 Co-infection**

Sofosbuvir used in combination with ribavirin was assessed in 223 HCV/HIV-1 co-infected subjects. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. 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.

### **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 .

### **Overdosage**

The highest documented dose of sofosbuvir was a single supra therapeutic dose of sofosbuvir 1,200 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.

## Storage and Handling Instructions

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

## Packaging Information

**HEPSITAJ Tablets** are available in a plastic container of 14 tablets.

**HEPSITAJ Tablets** are available in a plastic container of 28 tablets.

**HEPSITAJ-A.T\* Tablets** are available in plastic container of 10 & 30 tablets.

**Hepsitaj<sup>NEW</sup>**  
Sofosbuvir 400mg Tablets  
HEPATITIS C TREATMENT  
GENOTYPE 1, 2, 3, OR 4 INFECTION IN ADULTS  
A revolutionary treatment for Hep C

Hep C

HEPSITAJ is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C genotype 1, 2, 3, or 4 infection in adults.  
It is not known if HEPSITAJ is safe and effective in children under 18 years of age.  
With HEPSITAJ, there's hope that you can put Hep C behind you. You may be able to stop thinking about your disease, take the next step, and set a new course.

HEPSITAJ is sofosbuvir—a breakthrough medicine that directly targets the Hep C virus

\*In a clinical study of patients with Hep C genotypes 2 or 3 with and without prior Hep C treatment, the cure rate for patients with GT2 taking HEPSITAJ + ribavirin for 12 weeks was 93% (68 out of 73 patients studied) and the cure rate for patients with GT3 taking HEPSITAJ + ribavirin for 24 weeks was 84% (210 out of 250 patients studied). Cure means the Hep C virus is not detected in the blood when measured 3 months after treatment is completed.

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