

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOVALDI safely and effectively. See full prescribing information for SOVALDI.

SOVALDI® (sofosbuvir) tablets, for oral use  
Initial U.S. Approval: 2013

### RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 03/2015  
Warnings and Precautions (5.2) 11/2014

### INDICATIONS AND USAGE

SOVALDI 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. (1)

- SOVALDI 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. (1)

### DOSAGE AND ADMINISTRATION

- One 400 mg tablet taken once daily with or without food. (2.1)
- Should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of CHC. Recommended combination therapy: (2.1)

HCV Mono-infected and HCV/HIV-1 Co-infected	Treatment	Duration
Genotype 1 or 4	SOVALDI + peg-interferon alfa + ribavirin	12 weeks
Genotype 2	SOVALDI + ribavirin	12 weeks
Genotype 3	SOVALDI + ribavirin	24 weeks

- SOVALDI in combination with ribavirin for 24 weeks can be considered for CHC patients with genotype 1 infection who are interferon ineligible. (2.1)
- Should be used in combination with ribavirin for treatment of CHC in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first. (2.1)
- A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease. (2.4, 8.6)

### DOSAGE FORMS AND STRENGTHS

Tablets: 400 mg. (3)

### CONTRAINDICATIONS

- When used in combination with peginterferon alfa/ribavirin or ribavirin alone, all contraindications to peginterferon alfa and/or ribavirin also apply to SOVALDI combination therapy. (4)
- Because ribavirin may cause birth defects and fetal death, SOVALDI in combination with peginterferon alfa/ribavirin or

ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant. (4)

### WARNINGS AND PRECAUTIONS

- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone and SOVALDI in combination with another direct acting antiviral (DAA), particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with SOVALDI in combination with another DAA is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. (5.1, 6.2, 7.2)
- Pregnancy: Ribavirin may cause birth defects and fetal death and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least 2 effective methods of contraception and have monthly pregnancy tests. (5.2)

### ADVERSE REACTIONS

The most common adverse events (incidence greater than or equal to 20%, all grades) observed with SOVALDI in combination with ribavirin were fatigue and headache. The most common adverse events observed with SOVALDI in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Coadministration of amiodarone with SOVALDI in combination with another DAA may result in serious symptomatic bradycardia. (5.1, 6.2, 7.2)
- Drugs that are potent intestinal P-gp inducers (e.g., rifampin, St. John's wort) may alter the concentrations of sofosbuvir. (5.3, 7, 12.3)
- Consult the full prescribing information prior to use for potential drug-drug interactions. (5.1, 5.3, 7, 12.3)

### USE IN SPECIFIC POPULATIONS

- Patients with HCV/HIV-1 co-infection: Safety and efficacy have been studied. (8.8, 14.4)
- Patients with hepatocellular carcinoma awaiting liver transplantation: Safety and efficacy have been studied. (8.9)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose in Adults
- 2.2 Dose Modification
- 2.3 Discontinuation of Dosing
- 2.4 Severe Renal Impairment and End Stage Renal Disease

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Serious Symptomatic Bradycardia When Coadministered with Amiodarone and Another HCV Direct Acting Antiviral
- 5.2 Pregnancy: Use with Ribavirin or Peginterferon Alfa/Ribavirin
- 5.3 Use with Potent P-gp Inducers

### 6 ADVERSE REACTIONS

- 6.1 Adverse Reactions from Clinical Trials Experience

- 6.2 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Potential for Drug Interactions
- 7.2 Potentially Significant Drug Interactions
- 7.3 Drugs without Clinically Significant Interactions with SOVALDI

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Patients with HCV/HIV-1 Co-infection
- 8.9 Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation

- 8.10 Post-Liver Transplant Patients
- 8.11 CHC Patients with Genotype 5 or 6 HCV Infection

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- 13.2 Animal Toxicology and/or Pharmacology

**14 CLINICAL STUDIES**

- 14.1 Description of Clinical Trials
- 14.2 Clinical Trials in Subjects with Genotype 1 or 4 CHC
- 14.3 Clinical Trials in Subjects with Genotype 2 or 3 CHC
- 14.4 Clinical Trials in Subjects Co-infected with HCV and HIV-1

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

SOVALDI 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.

- SOVALDI 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 [See *Dosage and Administration (2)*, *Use in Specific Populations (8)* and *Clinical Studies (14)*].

The following points should be considered when initiating treatment with SOVALDI:

- Monotherapy of SOVALDI is not recommended for treatment of CHC.
- Treatment regimen and duration are dependent on both viral genotype and patient population [See *Dosage and Administration (2)*].
- Treatment response varies based on baseline host and viral factors [See *Use in Specific Populations (8)* and *Clinical Studies (14)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose in Adults

The recommended dose of SOVALDI is one 400 mg tablet, taken orally, once daily with or without food [See *Clinical Pharmacology (12.3)*].

SOVALDI 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 SOVALDI combination therapy is provided in Table 1.

**Table 1 Recommended Regimens and Treatment Duration for SOVALDI Combination Therapy in HCV Mono-infected and HCV/HIV-1 Co-infected Patients**

	Treatment	Duration
Patients with genotype 1 or 4 CHC	SOVALDI + peginterferon alfa <sup>a</sup> + ribavirin <sup>b</sup>	12 weeks
Patients with genotype 2 CHC	SOVALDI + ribavirin <sup>b</sup>	12 weeks
Patients with genotype 3 CHC	SOVALDI + ribavirin <sup>b</sup>	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.

SOVALDI 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 [See *Use in Specific Populations (8.8) and Clinical Studies (14.4)*]. 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

SOVALDI 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 [See *Use in Specific Populations (8.9)*].

## **2.2 Dose Modification**

Dose reduction of SOVALDI 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. 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 Coadministration with SOVALDI**

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

- The daily dose of ribavirin is administered orally in two divided doses with food.
- 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).

## **2.3 Discontinuation of Dosing**

If the other agents used in combination with SOVALDI are permanently discontinued, SOVALDI should also be discontinued.

## **2.4 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<sup>2</sup>) or with end stage

renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite [See *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

### 3 DOSAGE FORMS AND STRENGTHS

SOVALDI is available as a yellow colored, capsule-shaped, film-coated tablet debossed with “GSI” on one side and “7977” on the other side. Each tablet contains 400 mg sofosbuvir.

### 4 CONTRAINDICATIONS

When SOVALDI 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.

SOVALDI 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 [See *Warnings and Precautions (5.2) and Use in Specific Populations (8.1)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 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 SOVALDI 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 SOVALDI 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 SOVALDI 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 SOVALDI 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 SOVALDI 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 [*See Adverse Reactions (6.2), Drug Interactions (7.2)*].

## **5.2 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 [*See Contraindications (4)*]. 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 SOVALDI 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. [*See Contraindications (4) and Use in Specific Populations (8.1)*]. Refer also to the prescribing information for ribavirin.

## **5.3 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 SOVALDI. Rifampin and St. John's wort should not be used with SOVALDI [*See Drug Interactions (7.2)*].

# **6 ADVERSE REACTIONS**

## **6.1 Adverse Reactions from Clinical Trials Experience**

SOVALDI 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 SOVALDI is based on pooled Phase 3 clinical trial data (both controlled and uncontrolled) including 650 subjects who received SOVALDI + ribavirin (RBV) combination therapy for 12 weeks, 98 subjects who received SOVALDI + ribavirin

combination therapy for 16 weeks, 250 subjects who received SOVALDI + ribavirin combination therapy for 24 weeks, 327 subjects who received SOVALDI + 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 SOVALDI + ribavirin for 12 weeks, <1% for subjects receiving SOVALDI + ribavirin for 24 weeks, 11% for subjects receiving peginterferon alfa + ribavirin for 24 weeks and 2% for subjects receiving SOVALDI + peginterferon alfa + ribavirin for 12 weeks.

Treatment-emergent adverse events observed in  $\geq 15\%$  of subjects in clinical trials are provided in Table 3. 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 ( $\geq 20\%$ ) for SOVALDI + ribavirin combination therapy were fatigue and headache. The most common adverse events ( $\geq 20\%$ ) for SOVALDI + peginterferon alfa + ribavirin combination therapy were fatigue, headache, nausea, insomnia and anemia.

**Table 3 Treatment-Emergent Adverse Events (All Grades) Reported in  $\geq 15\%$  of Subjects in Any Treatment Arm**

	Interferon-free Regimens			Interferon-containing Regimens	
	PBO 12 weeks	SOVALDI + RBV <sup>a</sup> 12 weeks	SOVALDI + RBV <sup>a</sup> 24 weeks	Peg-IFN alfa + RBV <sup>b</sup> 24 weeks	SOVALDI + 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%

a. Subjects received weight-based ribavirin (1000 mg per day if weighing < 75 kg or 1200 mg per day if weighing  $\geq$  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 Table 3 occurred at severity of grade 1 in SOVALDI-containing regimens.

**Less Common Adverse Reactions Reported in Clinical Trials (<1%):** The following ADRs occurred in <1% of subjects receiving SOVALDI 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 Table 4. A side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

**Table 4 Percentage of Subjects Reporting Selected Hematological Parameters**

Hematological Parameters	Interferon-free Regimens			Interferon-containing Regimens	
	PBO 12 weeks	SOVALDI + RBV <sup>a</sup> 12 weeks	SOVALDI + RBV <sup>a</sup> 24 weeks	Peg-IFN + RBV <sup>b</sup> 24 weeks	SOVALDI + Peg-IFN + RBV <sup>a</sup> 12 weeks
	N=71	N=647	N=250	N=242	N=327
Hemoglobin (g/dL)					
< 10	0	8%	6%	14%	23%
< 8.5	0	1%	<1%	2%	2%
Neutrophils (x10 <sup>9</sup> /L)					
≥0.5 - < 0.75	1%	<1%	0	12%	15%
< 0.5	0	<1%	0	2%	5%
Platelets (x10 <sup>9</sup> /L)					
≥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 SOVALDI + peginterferon alfa + ribavirin 12 weeks group and in 1%, 3% and 3% of subjects in the peginterferon alfa + ribavirin 24 weeks, SOVALDI + ribavirin 12 weeks and SOVALDI + 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 10xULN was observed in <1%, 1% and 2% of subjects in the peginterferon alfa + ribavirin 24 weeks, SOVALDI + peginterferon alfa + ribavirin 12 weeks and SOVALDI + ribavirin 12 weeks groups, respectively.

Lipase Elevations

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

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of SOVALDI. 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 SOVALDI in combination with another HCV direct acting antiviral [See *Warnings and Precautions (5.1)*, *Drug Interactions (7.2)*].

## 7 DRUG INTERACTIONS

### 7.1 Potential for Drug Interactions

After oral administration of SOVALDI, 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 [See *Clinical Pharmacology (12.3)*]. 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 SOVALDI and thus should not be used with SOVALDI [See *Warnings and Precautions (5.3)*]. Coadministration of SOVALDI with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration; accordingly, SOVALDI 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 [See *Clinical Pharmacology (12.3)*].

### 7.2 Potentially Significant Drug Interactions

Drug interaction information for SOVALDI with potential concomitant drugs is summarized in Table 5. The drug interactions described are based on potential drug interactions that may occur with SOVALDI. The table is not all-inclusive [See *Warnings and Precautions (5.1,5.3)* and *Clinical Pharmacology (12.3)*].

**Table 5 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>Antiarrhythmics:</b> amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown	Coadministration of amiodarone with SOVALDI in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with SOVALDI in combination with another DAA is not recommended; if coadministration is required, cardiac monitoring is recommended [See <i>Warnings and Precautions</i> (5.1), <i>Adverse Reactions</i> (6.2)].
<b>Anticonvulsants:</b> carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended.
<b>Antimycobacterials:</b> rifabutin rifampin rifapentine	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended.  SOVALDI should not be used with rifampin, a potent intestinal P-gp inducer [See <i>Warnings and Precautions</i> (5.3)].
<b>Herbal Supplements:</b> St. John's wort ( <i>Hypericum perforatum</i> )	↓ sofosbuvir ↓ GS-331007	SOVALDI should not be used with St. John's wort, a potent intestinal P-gp inducer [See <i>Warnings and Precautions</i> (5.3)].
<b>HIV Protease Inhibitors:</b> tipranavir/ritonavir	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended.

a. This table is not all inclusive.

b. ↓ = decrease.

### 7.3 Drugs without Clinically Significant Interactions with SOVALDI

In addition to the drugs included in Table 5, the interaction between SOVALDI and the following drugs was evaluated in clinical trials and no dose adjustment is needed for either drug [See *Clinical Pharmacology* (12.3)]: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, oral contraceptives, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 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 [See *Warnings and Precautions (5.2)*].

**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. Healthcare providers and patients are encouraged to report such cases by calling Ribavirin Pregnancy Registry at 1-800-593-2214. For patients who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals, an Antiretroviral Pregnancy Registry is also available at 1-800-258-4263.**

#### *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 [See *Contraindications (4)*, *Warnings and Precautions (5.2)* and *ribavirin Package Insert*]. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans [See *peginterferon alfa Package Insert*].

#### Pregnancy Category B: SOVALDI

There are no adequate and well-controlled studies with SOVALDI 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.

### **8.3 Nursing Mothers**

It is not known whether SOVALDI 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.

### **8.4 Pediatric Use**

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

## 8.5 Geriatric Use

SOVALDI 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 SOVALDI is warranted in geriatric patients [See *Clinical Pharmacology* (12.3)].

## 8.6 Renal Impairment

No dose adjustment of SOVALDI is required for patients with mild or moderate renal impairment. The safety and efficacy of SOVALDI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m<sup>2</sup>) or end stage renal disease (ESRD) requiring hemodialysis. No dose recommendation can be given for patients with severe renal impairment or ESRD [See *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)]. Refer also to ribavirin and peginterferon alfa prescribing information for patients with CrCl <50 mL/min.

## 8.7 Hepatic Impairment

No dose adjustment of SOVALDI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) [See *Clinical Pharmacology* (12.3)]. Safety and efficacy of SOVALDI have not been established in patients with decompensated cirrhosis. See peginterferon alfa prescribing information for contraindication in hepatic decompensation.

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

The safety and efficacy of SOVALDI was assessed in 223 HCV/HIV-1 co-infected subjects [See *Clinical Studies* (14.4)]. See *Dosage and Administration* (2.1) 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 SOVALDI + ribavirin in Phase 3 trials [See *Adverse Reactions* (6.1)].

## 8.9 Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation

SOVALDI 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 SOVALDI 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 SOVALDI 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 SOVALDI 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  $\leq 14$ . Of these 61 subjects, 41 subjects underwent liver transplantation following up to 48 weeks of treatment with SOVALDI and ribavirin; 37 had HCV RNA  $< \text{LLOQ}$  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 SOVALDI and ribavirin in HCV-infected subjects prior to liver transplantation was comparable to that observed in subjects treated with SOVALDI and ribavirin in Phase 3 clinical trials.

### 8.10 Post-Liver Transplant Patients

The safety and efficacy of SOVALDI have not been established in post-liver transplant patients.

### 8.11 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.

## 10 OVERDOSAGE

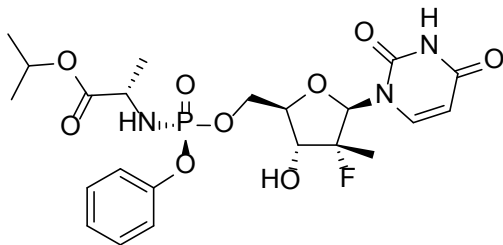
The highest documented dose of sofosbuvir was a single suprathreshold dose of sofosbuvir 1200 mg administered to 59 healthy subjects. In that trial, there were no untoward effects observed at this dose level, and adverse events were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups. The effects of higher doses are not known.

No specific antidote is available for overdose with SOVALDI. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with SOVALDI 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.

## 11 DESCRIPTION

SOVALDI is the brand name for sofosbuvir, 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  $\text{C}_{22}\text{H}_{29}\text{FN}_3\text{O}_9\text{P}$  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  $\geq 2$  mg/mL across the pH range of 2-7.7 at 37 °C and is slightly soluble in water.

SOVALDI tablets are for oral administration. Each tablet contains 400 mg of sofosbuvir. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus [See *Microbiology (12.4)*].

### 12.2 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, SOVALDI does not prolong QTc to any clinically relevant extent.

### 12.3 Pharmacokinetics

#### 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 SOVALDI, 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 SOVALDI 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, SOVALDI 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  $\mu\text{g/mL}$  to 20  $\mu\text{g/mL}$ . Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [ $^{14}\text{C}$ ]-sofosbuvir in healthy subjects, the blood to plasma ratio of  $^{14}\text{C}$ -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 [ $^{14}\text{C}$ ]-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 [ $^{14}\text{C}$ ]-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 [See *Use in Specific Populations (8.4)*].

### 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 [See *Use in Specific Populations (8.5)*].

### Patients with 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/1.73m<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 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 SOVALDI 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 [See *Dosage and Administration (2.4)* and *Use in Specific Populations (8.6)*].

### 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<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 SOVALDI is recommended for patients with mild, moderate and severe hepatic impairment [See *Use in Specific Populations (8.7)*].

### Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of sofosbuvir and GS-331007 are shown in Table 6. The effects of sofosbuvir on the exposure of coadministered drugs are shown in Table 7 [See *Drug Interactions (7.3)*].

**Table 6 Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug<sup>a</sup>**

Co-administered Drug	Dose of Coadministered Drug (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
					C <sub>max</sub>	AUC	C <sub>min</sub>
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 <sup>c</sup>	600 once daily	400 single dose	16	sofosbuvir	0.81 (0.60, 1.10)	0.94 (0.76, 1.16)	NA
Emtricitabine <sup>c</sup>	200 once daily						
Tenofovir disoproxil fumarate <sup>c</sup>	300 once daily			GS-331007	0.77 (0.70, 0.84)	0.84 (0.76, 0.92)	NA
Methadone	30 to 130 once daily	400 once daily	14	sofosbuvir	0.95 <sup>b</sup> (0.68, 1.33)	1.30 <sup>b</sup> (1.00, 1.69)	NA
				GS-331007	0.73 <sup>b</sup> (0.65, 0.83)	1.04 <sup>b</sup> (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. Comparison based on historic control
- c. Administered as ATRIPLA

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

**Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir<sup>a</sup>**

Coadministered Drug	Dose of Coadministered Drug (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered Drug PK With/Without Sofosbuvir No Effect=1.00		
				C <sub>max</sub>	AUC	C <sub>min</sub>
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 <sup>b</sup>	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.

## 12.4 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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  $\mu$ M; N=29), 0.029  $\mu$ M for genotype 2 (range 0.014-0.081  $\mu$ M; N=15) and 0.081  $\mu$ M for genotype 3a (range 0.024-0.181  $\mu$ M; N=106). In infectious virus assays, the EC<sub>50</sub> values of sofosbuvir against genotype 1a and 2a were 0.03 and 0.02  $\mu$ M, 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 SOVALDI 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.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Carcinogenesis and Mutagenesis**

*Use with Ribavirin and/or Peginterferon alfa:* Ribavirin was shown to be genotoxic in several *in vitro* and *in vivo* assays. Ribavirin was not oncogenic in a 6-month p53<sup>±</sup>-transgenic mouse study or a 2-year carcinogenicity study in rats. See the prescribing information for ribavirin.

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.

Two-year carcinogenicity studies in mice and rats were conducted with sofosbuvir. Mice were administered doses of up to 200 mg/kg/day in males and 600 mg/kg/day in females, while rats were administered doses of up to 750 mg/kg/day in males and females. No increase in the incidence of drug-related neoplasms were observed at the highest doses tested in mice and rats, resulting in AUC exposure to the predominant circulating metabolite GS-331007 of approximately 7- and 30-fold (in mice) and 13- and 17-fold (in rats), in males and females respectively, the exposure in humans at the recommended clinical dose.

#### **Impairment of Fertility**

*Use with Ribavirin and/or Peginterferon alfa:* In fertility studies in male animals, ribavirin induced reversible testicular toxicity, while peginterferon alfa may impair fertility in females. Refer to prescribing information for ribavirin and peginterferon alfa for additional information.

Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. At the highest dose tested, AUC exposure to the predominant circulating metabolite GS-331007 was approximately 8-fold the exposure in humans at the recommended clinical dose.

### **13.2 Animal Toxicology and/or Pharmacology**

Heart degeneration and inflammation were observed in rats following GS-9851 (a stereoisomeric mixture containing approximately 50% sofosbuvir) doses of 2000 mg/kg/day for up to 5 days. At this dose, AUC exposure to the predominant metabolite

GS-331007 is approximately 29-fold higher than human exposure at the recommended clinical dose. No heart degeneration or inflammation was observed in rats following sofosbuvir doses of up to 500 mg/kg/day for 6 months at a GS-331007 AUC exposure approximately 9-fold higher than human exposure at the recommended clinical dose. In dogs and mice, heart degeneration and inflammation were not observed following sofosbuvir doses of up to 500 and 1000 mg/kg/day for 9 and 3 months, respectively, the highest doses tested. At these doses, GS-331007 AUC exposures are approximately 27- and 41-fold higher, respectively, than human exposure at the recommended clinical dose.

## **14 CLINICAL STUDIES**

### **14.1 Description of Clinical Trials**

The safety and efficacy of SOVALDI was evaluated in five Phase 3 trials in a total of 1724 HCV mono-infected subjects with genotypes 1 to 6 chronic hepatitis C (CHC) and one Phase 3 trial in 223 HCV/HIV-1 co-infected subjects with genotype 1, 2 or 3 CHC. Among the five trials in HCV mono-infected subjects, one was conducted in treatment-naïve subjects with genotype 1, 4, 5 or 6 CHC in combination with peginterferon alfa 2a and ribavirin and the other four were conducted in subjects with genotype 2 or 3 CHC in combination with ribavirin, including one in treatment-naïve subjects, one in interferon intolerant, ineligible or unwilling subjects, one in subjects previously treated with an interferon-based regimen, and one in all subjects irrespective of prior treatment history or ability to take interferon. The trial in HCV/HIV-1 co-infected subjects was conducted in combination with ribavirin in treatment-naïve subjects with genotype 1 CHC and all subjects with genotype 2 or 3 CHC irrespective of prior treatment history or ability to take interferon. Subjects in these trials had compensated liver disease including cirrhosis. SOVALDI was administered at a dose of 400 mg once daily. The ribavirin (RBV) dose was weight-based at 1000-1200 mg daily administered in two divided doses when used in combination with SOVALDI, and the peginterferon alfa 2a dose, where applicable, was 180 micrograms per week. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels (no response guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL. Sustained virologic response (SVR) was the primary endpoint which was defined as HCV RNA less than LLOQ at 12 weeks after the end of treatment.

### **14.2 Clinical Trials in Subjects with Genotype 1 or 4 CHC**

#### Treatment-Naïve Adults – NEUTRINO (Study 110)

NEUTRINO was an open-label, single-arm trial that evaluated 12 weeks of treatment with SOVALDI in combination with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection compared to pre-specified historical control.

Treated subjects (N=327) had a median age of 54 years (range: 19 to 70); 64% of the subjects were male; 79% were White, 17% were Black; 14% were Hispanic or Latino;

mean body mass index was 29 kg/m<sup>2</sup> (range: 18 to 56 kg/m<sup>2</sup>); 78% had baseline HCV RNA greater than 6 log<sub>10</sub> IU per mL; 17% had cirrhosis; 89% had HCV genotype 1; 9% had HCV genotype 4 and 2% had HCV genotype 5 or 6. Table 8 presents the response rates for the treatment group of SOVALDI + peginterferon alfa + ribavirin.

**Table 8 Response Rates in Study NEUTRINO**

	SOVALDI + Peg-IFN alfa + RBV 12 weeks
	N=327 <sup>a</sup>
Overall SVR	90% (295/327)
Genotype 1 <sup>b</sup>	89% (261/292)
Genotype 1a	92% (206/225)
Genotype 1b	82% (54/66)
Genotype 4	96% (27/28)
Outcome for subjects without SVR	
On-treatment virologic failure	0/327
Relapse <sup>c</sup>	9% (28/326)
Other <sup>d</sup>	1% (4/327)

- Including seven subjects with genotype 5 or 6 infection.
- One subject had genotype 1a/1b mixed infection.
- The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
- Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 9.

**Table 9 SVR Rates for Selected Subgroups in NEUTRINO**

	SOVALDI + Peg-IFN alfa + RBV 12 weeks
Cirrhosis	
No	92% (252/273)
Yes	80% (43/54)
Race	
Black	87% (47/54)
Non-black	91% (248/273)
Multiple Baseline Factors	
Genotype 1, Metavir F3/F4 fibrosis, IL28B non-C/C, HCV RNA >800,000 IU/mL	71% (37/52)

SVR rates were 98% (93/95) in subjects with baseline IL28B C/C allele and 87% (202/232) in subjects with baseline IL28B non-C/C alleles.

It is estimated that the response rate in patients who previously failed pegylated interferon and ribavirin therapy will approximate the observed response rate in NEUTRINO subjects with multiple baseline factors traditionally associated with a lower response to interferon-based treatment (Table 9). The SVR rate in the NEUTRINO trial in genotype 1 subjects with IL28B non-C/C alleles, HCV RNA >800,000 IU/mL and Metavir F3/F4 fibrosis was 71% (37/52).

### 14.3 Clinical Trials in Subjects with Genotype 2 or 3 CHC

#### Treatment-Naïve Adults – FISSION (Study 1231)

FISSION was a randomized, open-label, active-controlled trial that evaluated 12 weeks of treatment with SOVALDI and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 2 and 3 HCV. The ribavirin doses used in the SOVALDI + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1000-1200 mg per day and 800 mg per day regardless of weight, respectively. Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence), HCV genotype (2 vs. 3) and baseline HCV RNA level (<6 log<sub>10</sub>IU/mL vs. ≥6 log<sub>10</sub>IU/mL). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio.

Treated subjects (N=499) had a median age of 50 years (range: 19 to 77); 66% of the subjects were male; 87% were White, 3% were Black; 14% were Hispanic or Latino; mean body mass index was 28 kg/m<sup>2</sup> (range: 17 to 52 kg/m<sup>2</sup>); 57% had baseline HCV RNA levels greater than 6 log<sub>10</sub> IU per mL; 20% had cirrhosis; 72% had HCV genotype 3. Table 10 presents the response rates for the treatment groups of SOVALDI + ribavirin and peginterferon alfa + ribavirin.

**Table 10 Response Rates in Study FISSION**

	<b>SOVALDI + RBV 12 weeks</b>	<b>Peg-IFN alfa + RBV 24 weeks</b>
	N=256 <sup>a</sup>	N=243 <sup>a</sup>
Overall SVR	67% (171/256)	67% (162/243)
Treatment difference <sup>b</sup>	0.3% (95% CI: -7.5% to 8.0%)	
Genotype 2	95% (69/73)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for subjects without SVR		
On-treatment virologic failure	<1% (1/256)	7% (18/243)
Relapse <sup>c</sup>	30% (76/252)	21% (46/217)
Genotype 2	5% (4/73)	15% (9/62)
Genotype 3	40% (72/179)	24% (37/155)
Other <sup>d</sup>	3% (8/256)	7% (17/243)

a. Including three subjects with recombinant genotype 2/1 HCV infection.

b. Adjusted for pre-specified stratification factors.

- c. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
- d. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for subjects with cirrhosis at baseline are presented in Table 11 by genotype.

**Table 11 SVR Rates by Cirrhosis and Genotype in Study FISSION**

	Genotype 2		Genotype 3	
	SOVALDI + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks	SOVALDI + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	N=73	N=67	N=183	N=176
Cirrhosis				
No	97% (59/61)	81% (44/54)	61% (89/145)	71% (99/139)
Yes	83% (10/12)	62% (8/13)	34% (13/38)	30% (11/37)

Interferon Intolerant, Ineligible or Unwilling Adults – POSITRON (Study 107)

POSITRON was a randomized, double-blinded, placebo-controlled trial that evaluated 12 weeks of treatment with SOVALDI and ribavirin (N=207) compared to placebo (N=71) in subjects who are interferon intolerant, ineligible or unwilling. Subjects were randomized in 3:1 ratio and stratified by cirrhosis (presence vs. absence).

Treated subjects (N=278) had a median age of 54 years (range: 21 to 75); 54% of the subjects were male; 91% were White, 5% were Black; 11% were Hispanic or Latino; mean body mass index was 28 kg/m<sup>2</sup> (range: 18 to 53 kg/m<sup>2</sup>); 70% had baseline HCV RNA levels greater than 6 log<sub>10</sub> IU per mL; 16% had cirrhosis; 49% had HCV genotype 3. The proportions of subjects who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most subjects had no prior HCV treatment (81%). Table 12 presents the response rates for the treatment groups of SOVALDI + ribavirin and placebo.

**Table 12 Response Rates in Study POSITRON**

	SOVALDI + RBV 12 weeks	Placebo 12 weeks
	N=207	N=71
Overall SVR	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
Outcome for subjects without SVR		
On-treatment virologic failure	0/207	97% (69/71)
Relapse <sup>a</sup>	20% (42/205)	0/0
Genotype 2	5% (5/107)	0/0
Genotype 3	38% (37/98)	0/0
Other <sup>b</sup>	2% (4/207)	3% (2/71)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 13 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

**Table 13 SVR Rates for Selected Subgroups by Genotype in POSITRON**

	SOVALDI + RBV 12 weeks	
	Genotype 2	Genotype 3
	N=109	N=98
Cirrhosis		
No	92% (85/92)	68% (57/84)
Yes	94% (16/17)	21% (3/14)
Interferon Classification		
Ineligible	88% (36/41)	70% (33/47)
Intolerant	100% (9/9)	50% (4/8)
Unwilling	95% (56/59)	53% (23/43)

Previously Treated Adults – FUSION (Study 108)

FUSION was a randomized, double-blinded trial that evaluated 12 or 16 weeks of treatment with SOVALDI and ribavirin in subjects who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence) and HCV genotype (2 vs. 3).

Treated subjects (N=201) had a median age of 56 years (range: 24 to 70); 70% of the subjects were male; 87% were White; 3% were Black; 9% were Hispanic or Latino; mean body mass index was 29 kg/m<sup>2</sup> (range: 19 to 44 kg/m<sup>2</sup>); 73% had baseline HCV RNA levels greater than 6log<sub>10</sub> IU per mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. Table 14 presents the response rates for the treatment groups of SOVALDI + ribavirin for 12 weeks and 16 weeks.

**Table 14 Response Rates in Study FUSION**

	<b>SOVALDI + RBV 12 weeks</b>	<b>SOVALDI + RBV 16 weeks</b>
	N= 103 <sup>a</sup>	N=98 <sup>a</sup>
Overall SVR	50% (51/103)	71% (70/98)
Genotype 2	82% (32/39)	89% (31/35)
Genotype 3	30% (19/64)	62% (39/63)
Outcome for subjects without SVR		
On-treatment virologic failure	0/103	0/98
Relapse <sup>b</sup>	48% (49/103)	29% (28/98)
Genotype 2	18% (7/39)	11% (4/35)
Genotype 3	66% (42/64)	38% (24/63)
Other <sup>c</sup>	3% (3/103)	0/98

a. Including six subjects with recombinant genotype 2/1 HCV infection.

b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

c. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 15 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

**Table 15 SVR Rates for Selected Subgroups by Genotype in Study FUSION**

	Genotype 2		Genotype 3	
	SOVALDI + RBV 12 weeks	SOVALDI + RBV 16 weeks	SOVALDI + RBV 12 weeks	SOVALDI + RBV 16 weeks
	N=39	N=35	N=64	N=63
Cirrhosis				
No	90% (26/29)	92% (24/26)	37% (14/38)	63% (25/40)
Yes	60% (6/10)	78% (7/9)	19% (5/26)	61% (14/23)
Response to prior HCV treatment				
Relapser/ breakthrough	86% (25/29)	89% (24/27)	31% (15/49)	65% (30/46)
Nonresponder	70% (7/10)	88% (7/8)	27% (4/15)	53% (9/17)

Treatment-Naïve and Previously Treated Adults – VALENCE (Study 133)

The VALENCE trial evaluated SOVALDI in combination with weight-based ribavirin for the treatment of genotype 2 or 3 HCV infection in treatment-naïve subjects or subjects who did not achieve SVR with prior interferon-based treatment, including subjects with compensated cirrhosis. The original trial design was a 4 to 1 randomization to SOVALDI + ribavirin for 12 weeks or placebo. Based on emerging data, this trial was unblinded and all genotype 2 HCV-infected subjects continued the original planned treatment and received SOVALDI + ribavirin for 12 weeks, and duration of treatment with SOVALDI + ribavirin in genotype 3 HCV-infected subjects was extended to 24 weeks. Eleven genotype 3 subjects had already completed SOVALDI + ribavirin for 12 weeks at the time of the amendment.

Treated subjects (N=419) had a median age of 51 years (range: 19 to 74); 60% of the subjects were male; mean body mass index was 26 kg/m<sup>2</sup> (range: 17 to 44 kg/m<sup>2</sup>); the mean baseline HCV RNA level was 6.4 log<sub>10</sub> IU per mL; 78% had HCV genotype 3; 58% of the subjects were treatment-experienced and 65% of those subjects experienced relapse/breakthrough to prior HCV treatment.

Table 16 presents the response rates for the treatment groups of SOVALDI + ribavirin for 12 weeks and 24 weeks.

**Table 16 Response Rates in Study VALENCE<sup>a</sup>**

	<b>Genotype 2 SOVALDI + RBV 12 weeks</b>	<b>Genotype 3 SOVALDI + RBV 24 weeks</b>
	N=73	N=250
Overall SVR	93% (68/73)	84% (210/250)
Outcome for subjects without SVR		
On-treatment virologic failure	0% (0/73)	<1% (1/250)
Relapse <sup>b</sup>	7% (5/73)	14% (34/249)
Treatment-naïve	3% (1/32)	5% (5/105)
Treatment-experienced	10% (4/41)	20% (29/144)
Other <sup>c</sup>	0% (0/73)	2% (5/250)

- Placebo subjects (N=85) were not included as none achieved SVR12. Eleven genotype 3 subjects who received SOVALDI + ribavirin for 12 weeks were not included.
- The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on treatment assessment.
- Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow up).

Table 17 presents the subgroup analysis by genotype for cirrhosis and prior HCV treatment experience.

**Table 17 SVR Rates for Selected Subgroup by Genotype in Study VALENCE**

	<b>Genotype 2 SOVALDI + RBV 12 weeks</b>	<b>Genotype 3 SOVALDI + RBV 24 weeks</b>
	N=73	N=250
Treatment-naïve	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	93% (86/92)
Cirrhotic	100% (2/2)	92% (12/13)
Treatment-experienced	90% (37/41)	77% (112/145)
Non-cirrhotic	91% (30/33)	85% (85/100)
Cirrhotic	88% (7/8)	60% (27/45)

#### 14.4 Clinical Trials in Subjects Co-infected with HCV and HIV-1

SOVALDI was studied in an open-label clinical trial (Study PHOTON-1) evaluating the safety and efficacy of 12 or 24 weeks of treatment with SOVALDI and ribavirin in subjects with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV-1. Genotype 2 and 3 subjects were either HCV treatment-naïve or experienced, whereas genotype 1 subjects were all treatment-naïve. Subjects received 400 mg SOVALDI and weight-based ribavirin (1000 mg for subjects weighing <75 kg or 1200 mg for subjects weighing ≥75kg) daily for 12 or 24 weeks based on genotype and prior treatment history. Subjects were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm<sup>3</sup>

or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm<sup>3</sup>. Efficacy data 12 weeks post treatment are available for 210 subjects (see Table 18).

**Table 18 Response Rates in Study PHOTON-1<sup>a</sup>**

	HCV genotype 1	HCV genotype 2	HCV genotype 3
	<b>SOVALDI + RBV 24 weeks TN (N=114)</b>	<b>SOVALDI + RBV 12 weeks TN (N=26)</b>	<b>SOVALDI + RBV 24 weeks TE (N=13)</b>
Overall	76% (87/114)	88% (23/26)	92% (12/13)
Outcome for subjects without SVR12			
On-treatment virologic failure	1% (1/114)	4% (1/26)	0/13
Relapse <sup>b</sup>	22% (25/113)	0/25	8% (1/13)
Other <sup>c</sup>	1% (1/114)	8% (2/26)	0/13

TN = Treatment-naïve; TE = Treatment-experienced

- Subjects with genotype 2 CHC treated with SOVALDI + RBV for 24 weeks (N=15) and subjects with genotype 3 CHC treated with SOVALDI + RBV for 12 weeks (N=42) are not included in the table.
- The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on treatment assessment.
- Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow up).

In subjects with HCV genotype 1 infection, the SVR rate was 82% (74/90) in subjects with genotype 1a infection and 54% (13/24) in subjects with genotype 1b infection, with relapse accounting for the majority of treatment failures. SVR rates in subjects with HCV genotype 1 infection were 80% (24/30) in subjects with baseline IL28B C/C allele and 75% (62/83) in subjects with baseline IL28B non-C/C alleles.

In the 223 CHC subjects with HIV-1 co-infection, the percentage of CD4+ cells did not change during treatment. Median CD4+ cell count decreases of 85 cells/mm<sup>3</sup> and 84 cells/mm<sup>3</sup> were observed at the end of treatment with SOVALDI + ribavirin for 12 or 24 weeks, respectively. HIV-1 rebound during SOVALDI + ribavirin treatment occurred in 2 subjects (0.9%) on antiretroviral therapy.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

SOVALDI tablets are yellow, capsule-shaped, film-coated tablets containing 400 mg sofosbuvir debossed with “GSI” on one side and “7977” on the other side. Each bottle contains 28 tablets (NDC 61958-1501-1), a silica gel desiccant, polyester coil and is closed with a child-resistant closure.

Store at room temperature below 30 °C (86 °F).

- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### **Pregnancy**

Ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Ribavirin therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately before starting therapy. When SOVALDI is used in combination with peginterferon/ribavirin or ribavirin, patients must be advised of the teratogenic/embryocidal risks of ribavirin and should be advised that extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients both during treatment and for 6 months after the completion of treatment [See *Contraindications (4) and Warnings and Precautions (5.2)*].

Women of childbearing potential and their male partners must use at least two forms of effective contraception during treatment and for 6 months after the treatment has been stopped; routine monthly pregnancy tests must be performed during this time.

Patients should be advised to notify their health care provider immediately in the event of a pregnancy. There is a Ribavirin Pregnancy Registry established to monitor maternal and fetal outcomes of pregnant women exposed to ribavirin. Patients should be encouraged to register by calling 1-800-593-2214. For patients who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals, an Antiretroviral Pregnancy Registry is also available at 1-800-258-4263.

### **Hepatitis C Virus Transmission**

Patients should be informed 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.

### **Administration**

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

Patients should be advised that the dose of SOVALDI must not be reduced and it should be taken on a regular dosing schedule with or without food. If a patient did not take the SOVALDI at the regular time, it could be taken later in the day. However, no more than 400 mg of SOVALDI should be taken on any calendar day. The patient should resume the regular dosing schedule on the next day.

Manufactured and distributed by:  
Gilead Sciences, Inc.

Foster City, CA 94404

SOVALDI is a trademark of Gilead Sciences, Inc., or its related companies. ATRIPLA is a trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. All other trademarks referenced herein are the property of their respective owners.

©2015 Gilead Sciences, Inc. All rights reserved.

204671-GS-002

**Patient Information**  
**SOVALDI® (soh-VAHL-dee)**  
**(sofosbuvir)**  
**tablets**

Read this Patient Information before you start taking SOVALDI and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

SOVALDI is used in combination with other antiviral medicines. When taking SOVALDI with ribavirin or in combination with peginterferon alfa and ribavirin you should also read those Medication Guides.

The information in this Patient Information Leaflet talks about SOVALDI when it is used with ribavirin and in combination with peginterferon alfa and ribavirin.

**What is the most important information I should know about SOVALDI?**

**SOVALDI, in combination with ribavirin or peginterferon alfa and ribavirin, may cause birth defects or death of your unborn baby.** If you are pregnant or your sexual partner is pregnant or plans to become pregnant, do not take these medicines. You or your sexual partner should not become pregnant while taking SOVALDI with ribavirin or in combination with peginterferon alfa and ribavirin, and for 6 months after treatment is over.

- **Females and males must use 2 effective forms of birth control during treatment and for the 6 months after treatment with SOVALDI and ribavirin or in combination with peginterferon alfa and ribavirin.** Talk to your healthcare provider about forms of birth control that may be used during this time.
- Females must have a negative pregnancy test before starting treatment with SOVALDI and ribavirin or in combination with peginterferon alfa and ribavirin, every month while being treated, and for 6 months after your treatment ends.
- If you or your female sexual partner becomes pregnant while taking or within 6 months after you stop taking SOVALDI and ribavirin, or SOVALDI in combination with peginterferon alfa and ribavirin, tell your healthcare provider right away. You or your healthcare provider should contact the Ribavirin Pregnancy Registry by calling 1-800-593-2214. The Ribavirin Pregnancy Registry collects information about what happens to mothers and their babies if the mother takes ribavirin while she is pregnant. If you are also infected with HIV and taking medicines to treat your HIV infection, an Antiretroviral Pregnancy Registry is also available at 1-800-258-4263.

**You should not take SOVALDI alone.** SOVALDI should be used together with ribavirin or in combination with peginterferon alfa and ribavirin to treat chronic hepatitis C infection.

## What is SOVALDI?

- SOVALDI is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C infection in adults.
- SOVALDI should not be taken alone.

It is not known if SOVALDI is safe and effective in children under 18 years of age.

## Who should not take SOVALDI?

See **“What is the most important information I should know about SOVALDI?”**

## What should I tell my healthcare provider before taking SOVALDI?

### Before taking SOVALDI, tell your healthcare provider if you:

- have liver problems other than hepatitis C infection
- have had a liver transplant
- have severe kidney problems or you are on dialysis
- have HIV
- have any other medical condition
- are breastfeeding or plan to breastfeed. It is not known if SOVALDI passes into your breast milk. You and your healthcare provider should decide if you will take SOVALDI or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Other medicines may affect how SOVALDI works.

### Especially tell your healthcare provider if you take any of the following medicines:

- amiodarone (Cordarone<sup>®</sup>, Nexterone<sup>®</sup>, Pacerone<sup>®</sup>)
- carbamazepine (Carbatrol<sup>®</sup>, Epitol<sup>®</sup>, Equetro<sup>®</sup>, Tegretol<sup>®</sup>)
- oxcarbazepine (Trileptal<sup>®</sup>, Oxtellar XR<sup>™</sup>)
- phenytoin (Dilantin<sup>®</sup>, Phenytek<sup>®</sup>)
- phenobarbital (Luminal<sup>®</sup>)
- rifabutin (Mycobutin<sup>®</sup>)
- rifampin (Rifadin<sup>®</sup>, Rifamate<sup>®</sup>, Rifater<sup>®</sup>, Rimactane<sup>®</sup>)
- rifapentine (Priftin<sup>®</sup>)

- St. John's wort (*Hypericum perforatum*) or a product that contains St. John's wort
- tipranavir (Aptivus<sup>®</sup>)

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

### **How should I take SOVALDI?**

- Take 1 tablet of SOVALDI 1 time each day only, with or without food.
- Take SOVALDI exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking SOVALDI without first talking with your healthcare provider. If you think there is a reason to stop taking SOVALDI, talk to your healthcare provider before doing so.
- If you miss a dose of SOVALDI, take the missed dose as soon as you remember the same day. Do not take more than 1 tablet (400 mg) of SOVALDI in a day. Take your next dose of SOVALDI at your regular time the next day.
- If you take too much SOVALDI, call your healthcare provider or go to the nearest hospital emergency room right away.

### **What are the possible side effects of SOVALDI?**

See **“What is the most important information I should know about SOVALDI?”**

The most common side effects of SOVALDI when used in combination with ribavirin include:

- tiredness
- headache

The most common side effects of SOVALDI when used in combination with peginterferon alfa and ribavirin include:

- tiredness
- headache
- nausea
- difficulty sleeping
- low red blood cell count

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of SOVALDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store SOVALDI?**

- Store SOVALDI at room temperature below 86°F (30°C).
- Keep SOVALDI in its original container.
- Do not use SOVALDI if the seal over the bottle opening is broken or missing.

**Keep SOVALDI and all medicines out of the reach of children.**

### **General information about the safe and effective use of SOVALDI**

It is not known if treatment with SOVALDI will prevent you from infecting another person with the hepatitis C virus during treatment. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SOVALDI for a condition for which it was not prescribed. Do not give SOVALDI to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information about SOVALDI, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about SOVALDI that is written for health professionals.

For more information, call 1-800-445-3235 or go to [www.SOVALDI.com](http://www.SOVALDI.com).

### **What are the ingredients in SOVALDI?**

**Active ingredient:** sofosbuvir

**Inactive ingredients:** colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose.

The tablet film-coat contains: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured and distributed by:  
Gilead Sciences, Inc.  
Foster City, CA 94404

Issued: March 2015

SOVALDI and HARVONI are trademarks of Gilead Sciences, Inc., or its related companies. All other trademarks referenced herein are the property of their respective owners.

©2015 Gilead Sciences, Inc. All rights reserved.

204671-GS-002