Product Monograph

PrSOVALDI®

(sofosbuvir) tablets

400 mg sofosbuvir

Antiviral Agent

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SOVALDI®
sofosbuvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 400 mg sofosbuvir	None

*For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

SOVALDI (sofosbuvir) is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of genotype 1, 2, 3, or 4 chronic hepatitis C virus (CHC) infection as a component of a combination antiviral treatment regimen.

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

- SOVALDI must not be administered as monotherapy (see **WARNINGS AND PRECAUTIONS**, **General**).
- Treatment regimen and duration are dependent on both viral genotype and patient population (see **DOSAGE AND ADMINISTRATION**).
- Treatment response varies based on baseline host and viral factors.

Geriatrics (> 65 years of age):

Clinical studies of SOVALDI involving patients aged 65 and over showed similar treatment response rates to that of younger subjects across treatment groups. In general, caution should be exercised when administering SOVALDI in elderly patients, reflecting the greater frequency of anemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (see **WARNINGS AND PRECAUTIONS**).

Pediatrics (< 18 years of age):

Safety and effectiveness in pediatric patients have not been established (see **WARNINGS AND PRECAUTIONS**).

Patients Awaiting Liver Transplantation:

SOVALDI efficacy with SOVALDI + ribavirin (RBV) regimen has been established in patients with HCV genotype 1, 2, 3 or 4 infection awaiting liver transplantation with

hepatocellular carcinoma (HCC) meeting Milan criteria (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

Patients Co-infected with HIV-1:

SOVALDI efficacy with SOVALDI + RBV regimen has been established in treatment-naïve CHC patients with HCV genotype 1 and in CHC patients with HCV genotype 2 or 3 regardless of treatment experience. Clinical data is not available for treatment-experienced HCV genotype 1 patients or HCV genotype 4 patients (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

CONTRAINDICATIONS

SOVALDI is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

When SOVALDI is used in combination with peginterferon alfa/ribavirin or ribavirin, the contraindications applicable to those agents are applicable to combination therapies. Refer to the Product Monographs of peginterferon alfa and ribavirin for a list of their contraindications.

SOVALDI combination treatment with peginterferon alfa/ribavirin or ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant or may become pregnant because of the risks for birth defects and fetal death associated with ribavirin (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Potential for Hepatitis B Virus (HBV) Reactivation**

Screen all patients for evidence of current or prior HBV infection before initiating SOVALDI treatment. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct acting antivirals (DAAs) in patients co-infected with HBV (see **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**).

General

SOVALDI must not be administered as a monotherapy and must only be used in combination with either peginterferon alfa/ribavirin or ribavirin for the treatment of hepatitis C infection. Therefore, the Product Monographs for these agents must be consulted before starting

treatment with SOVALDI. The S282T substitution in NS5B, associated with resistance to sofosbuvir, was detected in one subject who received SOVALDI monotherapy (see **MICROBIOLOGY**, **Resistance**).

If peginterferon alfa/ribavirin or ribavirin used in combination with SOVALDI is permanently discontinued, SOVALDI must also be discontinued (see **DOSAGE AND ADMINISTRATION**).

Use with Potent P-gp Inducers

Drugs that are potent P-gp inducers in the intestine (eg, rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of SOVALDI and potential loss of virologic response. Rifampin and St. John's wort should not be used with SOVALDI (see **DRUG INTERACTIONS**).

Cardiovascular

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 taking amiodarone who was coadministered 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 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 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, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Coadministration with Related Products

SOVALDI should not be administered concurrently with other medicinal products containing sofosbuvir (eg, HARVONI, EPCLUSA®, VOSEVI®).

Potential for Hepatitis B Virus Reactivation

Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV co-infected patients who were undergoing, or completed treatment with DAAs. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patients with serologic evidence of resolved HBV infection (ie, HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Hepatic/Biliary/Pancreatic

No dose adjustment of SOVALDI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). Safety and efficacy of SOVALDI have not been established in patients with decompensated cirrhosis.

Renal

No dose adjustment of SOVALDI is required for patients with mild or moderate renal impairment. The safety and efficacy of SOVALDI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women:
There are no data on the use of SOVALDI in pregnant women. No effects on fetal development with sofosbuvir have been observed in rats and rabbits at the highest doses

tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 10-fold and 28-fold the exposure in humans at the recommended clinical dose, respectively (see **TOXICOLOGY**).

Ribavirin may cause birth defects and/or death of the exposed fetus and significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients (see **CONTRAINDICATIONS**). 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 6 months after the treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Refer to the Product Monograph containing ribavirin information for additional guidance.

Nursing Women:

It is not known whether sofosbuvir and its metabolites are excreted in human breast milk. Excretion of sofosbuvir in milk was studied in postpartum female rats after a single oral dose. The milk:plasma concentration ratios in the female rats were 0.1 at 1 hour post-dose and 0.8 at 24 hours post-dose. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats. Mothers should be instructed not to breast-feed if they are taking SOVALDI. See also the Product Monograph containing ribavirin information.

Pediatrics (< 18 years of age):

The safety and efficacy of SOVALDI in pediatric patients have not been established.

Geriatrics (> 65 years of age):

Clinical studies of SOVALDI included 99 subjects (90 subjects received SOVALDI) 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. In general, caution should be exercised when administering SOVALDI in elderly patients reflecting the greater frequency of anemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Patients with Genotype 5 or 6 CHC:

There is limited data regarding the use of SOVALDI in patients with genotype 5 or 6 CHC. Seven patients infected with genotype 5 (n=1) or genotype 6 (n=6) were included in the NEUTRINO clinical trial. Following 12 weeks of treatment with SOVALDI in combination with peginterferon alfa/ribavirin, all 7 patients achieved SVR12.

HCV/HBV Co-Infection:

The safety and efficacy of SOVALDI have not been established in patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

Post-Liver Transplant Patients:

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

Monitoring and Laboratory Tests

Clearance of HCV may lead to increased replication of HBV in patients who are co-infected with HCV and HBV; co-infected patients should be monitored for clinical and laboratory signs (eg, HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

As liver function may improve during treatment with SOVALDI, monitoring of certain laboratory parameters and/or concomitant medications may be required. For guidance see **DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Other Forms of Interactions.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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, 250 subjects who received SOVALDI + ribavirin combination therapy for 24 weeks, 327 subjects who received SOVALDI + peginterferon (PEG) 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.

No adverse drug reactions specific to SOVALDI have been identified. Table 1 lists adverse reactions (Grade 2 and higher) observed in clinical trials of SOVALDI combination therapy that occurred in greater than or equal to 3% of subjects in any of the treatment arms. The most common adverse reaction (≥ 5%) for SOVALDI + ribavirin combination therapy (12 weeks or 24 weeks treatment) was fatigue. The most common adverse reactions (≥ 5%) for SOVALDI + peginterferon alfa + ribavirin combination therapy were fatigue, anemia, neutropenia, insomnia, headache and nausea.

Table 1. Treatment-Emergent Adverse Drug Reactions (Grade 2 and Higher) Reported in at Least 3% of Subjects in Any Treatment Arm[a,b]

	PBO (N=71)	SOVALDI +RBV 12 weeks (N=650)	SOVALDI +RBV 24 weeks (N=250)	PEG+RBV 24 weeks (N=243)	SOVALDI +PEG+RBV 12 weeks (N=327)
Fatigue	4 (5.6%)	49 (7.5%)	13 (5.2%)	42 (17.3%)	39 (11.9%)
Anaemia	0	31 (4.8%)	7 (2.8%)	14 (5.8%)	46 (14.1%)
Insomnia	1 (1.4%)	19 (2.9%)	11 (4.4%)	22 (9.1%)	20 (6.1%)
Headache	0	22 (3.4%)	7 (2.8%)	15 (6.2%)	26 (8.0%)
Neutropenia	0	1 (0.2%)	0	23 (9.5%)	40 (12.2%)
Nausea	0	16 (2.5%)	4 (1.6%)	10 (4.1%)	18 (5.5%)
Irritability	0	10 (1.5%)	3 (1.2%)	13 (5.3%)	12 (3.7%)
Pruritus	0	7 (1.1%)	10 (4.0%)	8 (3.3%)	8 (2.4%)
Dyspnea	0	11 (1.7%)	5 (2.0%)	3 (1.2%)	13 (4.0%)
Depression	0	7 (1.1%)	2 (0.8%)	17 (7.0%)	5 (1.5%)
Influenza like illness	0	3 (0.5%)	2 (0.8%)	11 (4.5%)	11 (3.4%)
Decreased appetite	1 (1.4%)	7 (1.1%)	1 (0.4%)	12 (4.9%)	5 (1.5%)
Thrombocytopenia	1 (1.4%)	0	0	19 (7.8%)	6 (1.8%)
Myalgia	0	7 (1.1%)	2 (0.8%)	9 (3.7%)	6 (1.8%)
Rash	1 (1.4%)	3 (0.5%)	1 (0.4%)	11 (4.5%)	7 (2.1%)
Asthenia	0	3 (0.5%)	12 (4.8 %)	2 (0.8%)	3 (0.9%)

a Frequencies of adverse drug reactions are based on Grade 2 and higher treatment-emergent adverse events, considered related to study drug.

b Additionally, the following adverse drug reactions of low severity (Grade 1) occurred with SOVALDI + ribavirin combination therapy: dry skin (5%), nasopharyngitis (4%).

Less Common Clinical Trial Adverse Drug Reactions (<3%)

Treatment-emergent, related (to any active treatment) adverse drug reactions of at least moderate intensity (Grade 2 and higher) occurring in less than 3% of patients receiving SOVALDI are listed below by body system:

Table 2. Treatment-Emergent Adverse Drug Reactions (Grade 2 and Higher) Reported in < 3% of Subjects Receiving SOVALDI

Body System	SOVALDI + RBV	SOVALDI + PEG-IFN + RBV
Blood and Lymphatic System Disorders	Lymphadenopathy, lymphopenia, neutropenia	Hemolytic anemia, leukopenia, thrombocytopenia
Ear And Labyrinth Disorders	Vertigo	N/A
Cardiac Disorders	Palpitations	N/A
Eye Disorders	Amaurosis Fugax, dry eye, eye irritation, visual impairment	Vision blurred
Gastrointestinal Disorders	Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, anal inflammation, constipation, diarrhea, dry mouth, dyspepsia, epigastric discomfort, frequent bowel movements, gastritis, gastroesophageal reflux disease, nausea, stomatitis, tongue ulceration, toothache, vomiting	Abdominal pain, abdominal pain lower, abdominal pain upper, aphthous stomatitis, cheilitis, constipation, diarrhea, dyspepsia, gastroesophageal reflux disease, glossitis, vomiting
General Disorders and Administration Site Conditions	Asthenia, chest pain, chills, feeling abnormal, feeling cold, influenza like illness, irritability, malaise, nodule, oedema peripheral, pain, pyrexia, xerosis	Asthenia, chest discomfort, chills, feeling abnormal, injection site rash, injection site reaction, pain, pyrexia, spinal pain
Hepatobiliary Disorders	Hyperbilirubinaemia	Hyperbilirubinaemia
Immune System Disorders	Sarcoidosis	Cryoglobulinaemia
Infections and Infestations	Bronchitis, fungal infection, kidney infection, nasopharyngitis, oral herpes, upper respiratory tract infection, urinary tract infection, varicella	Folliculitis, gastroenteritis viral, infected skin ulcer, skin bacterial infection, urinary tract infection
Injury, Poisoning and Procedural Complications	Excoriation, sunburn, wound	N/A
Investigations	Blood glucose increased, eosinophil count increased, hemoglobin abnormal, hemoglobin decreased, heart rate increased, thyroid function test abnormal, weight decreased	Blood creatinine increased, blood uric acid increased, hemoglobin abnormal, hemoglobin decreased, neutrophil count decreased, platelet count decreased, transaminases increased, weight decreased
Metabolism and Nutrition Disorders	Decreased appetite, hyperglycemia, hypokalemia, increased appetite	Decreased appetite, hyperglycemia, hyponatremia
Musculoskeletal And Connective Tissue Disorders	Arthralgia, flank pain, muscle spasms, muscle twitching, myalgia, pain in extremity	Arthralgia, back pain, muscle spasms, muscular weakness, myalgia

Body System	SOVALDI + RBV	SOVALDI + PEG-IFN + RBV
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Basal cell carcinoma	N/A
Nervous System Disorders	Amnesia, burning sensation, disturbance in attention, dizziness, dysgeusia, lethargy, memory impairment, migraine, nerve root compression, neuropathy peripheral, paresis, restless legs syndrome	Ageusia, amnesia, disturbance in attention, dizziness, dizziness postural, dysgeusia, loss of consciousness, mental impairment, migraine, sinus headache, tremor
Psychiatric Disorders	Abnormal dreams, aggression, agitation, anxiety, apathy, confusional state, depressed mood, depression, hallucination, libido decreased, libido increased, mood altered, mood swings, nightmare, sleep disorder, suicidal ideation, suicide attempt, thinking abnormal	Affect lability, agitation, anxiety, confusional state, depression, distractibility, libido decreased, mood swings, restlessness, tachyphrenia
Renal and Urinary Disorders	Renal failure	N/A
Reproductive System and Breast Disorders	N/A	Pelvic pain
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, dyspnoea at rest, dyspnea exertional, nasal dryness, oropharyngeal pain	Cough, nasal dryness
Skin And Subcutaneous Tissue Disorders	Alopecia, asteatosis, dermatitis, dry skin, eczema, erythema, hyperhidrosis, night sweats, onychoclasis, photosensitivity reaction, pruritus, pruritus generalised, psoriasis, rash, rash generalised, rash macular, rash maculo-papular, rash papular, skin fissures	Dermatitis, pruritus, psoriasis, rash, rash generalised, rash maculo-papular, urticarial
Vascular Disorders	Hematoma, hot flush	Hot flush, hypertension

Special Populations

HIV-1 Co-infected Patients

The safety profile of SOVALDI and ribavirin in HIV-1 co-infected subjects was similar to that observed in mono-infected HCV subjects treated with SOVALDI and ribavirin in Phase 3 clinical trials. Additionally, dizziness (Grades 2-4) was observed in >5% of HIV-1 co-infected subjects (see **CLINICAL TRIALS**).

Patients Awaiting Liver Transplantation

The safety profile of SOVALDI and ribavirin in HCV-infected subjects prior to liver transplantation was similar to that observed in subjects treated with SOVALDI and ribavirin in Phase 3 clinical trials (see **CLINICAL TRIALS**).

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

The frequency of treatment-emergent laboratory abnormalities (Grades 3-4) occurring in at least 2% of subjects in any treatment arm are described in Table 3.

Table 3. Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Subjects in Any Treatment Arm

Laboratory Abnormality Parameters	PBO 12 weeks	SOVALDI + RBV[a] 12 weeks	SOVALDI+ RBV[a] 24 weeks	Peg-IFN + RBV[b] 24 weeks	SOVALDI+ Peg-IFN + RBV[a] 12 weeks
	N=71	N=650	N=250	N=243	N=327
Hemoglobin[c] (< 9 g/dL or change from baseline ≥ 4.5 g/dL)	0	9%	11%	10%	27%
Neutrophils (< 0.75 x10^9/L)	1%	< 1%	0	15%	20%
Platelets (< 50 x10^9/L)	3%	< 1%	1%	7%	< 1%
Lymphocytes (< 0.5 x10^3/μL)	0	1%	2%	11%	5%
White blood cells (< 1.5 x10^3/μL)	0	<1%	0	5%	6%
ALT (> 5 x ULN)	9%	<1%	1%	4%	2%
AST (> 5 x ULN)	14%	<1%	0	2%	3%
Lipase (> 3 x ULN)	1%	2%	2%	2%	< 1%
Serum glucose (> 250 mg/dL)	6%	2%	1%	2%	2%
Total bilirubin (> 2.5 x ULN)	0	3%	3%	1%	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.

c Grade 4 hemoglobin abnormality (<7 g/dL) occurred in 1 subject in the SOVALDI+Peg-IFN+RBV treatment arm.

Post-Market Adverse Drug Reactions

In addition to adverse reactions from clinical studies, 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 when amiodarone is coadministered with SOVALDI in combination with another HCV DAA (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **DRUG INTERACTIONS**).

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Sofosbuvir is a nucleotide prodrug. 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 **ACTION AND CLINICAL PHARMACOLOGY**). 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 (eg, 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**). 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 relevant inhibitors of drug transporters including P-gp, BCRP, OATP1B1 and OATP1B3 or enzymes CYP3A4, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2C8, CYP2D6, and UGT1A1 and thus are not expected to increase exposures of drugs that are substrates of these transporters or enzymes (see **DETAILED PHARMACOLOGY**).

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 **ACTION AND CLINICAL PHARMACOLOGY**).

Drug interaction information for SOVALDI with potential concomitant drugs is summarized in Table 4. The drug interactions described are based on potential drug interactions that may occur with SOVALDI. The table is not all-inclusive (see **CONTRAINDICATIONS** and **ACTION AND CLINICAL PHARMACOLOGY**)

Table 4. Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrthymics: 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 **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
Anticonvulsants: carbamazepine phenytoin phenobarbital	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with carbamazepine, phenytoin or phenobarbital is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended.
Antimycobacterials: rifampin rifapentine*	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended. SOVALDI should not be used with rifampin, a potent intestinal P-gp inducer (see **WARNINGS AND PRECAUTIONS, General, Use with Potent P-gp Inducers**)

*Drug not marketed in Canada.

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease, ↔ no effect

Drug-drug interaction studies with SOVALDI and HCV protease inhibitors (boceprevir and telaprevir) have not been conducted; therefore there are no data to support a dosing recommendation for the use of SOVALDI in combination with these agents.

Drugs without Clinically Significant Interactions with SOVALDI

Based on drug interaction studies conducted with SOVALDI, no clinically significant drug interactions have been either observed or are expected when SOVALDI is combined with the following drugs: cyclosporine, darunavir/ritonavir, emtricitabine, efavirenz, methadone, oral contraceptives, oxcarbazepine, raltegravir, rifabutin, rilpivirine, tacrolimus (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**, **Other Forms of Interactions**), or tenofovir disoproxil fumarate.

Other Forms of Interactions

As liver function may improve due to treatment of HCV with DAAs, it is recommended to closely monitor:

- the International Normalized Ratio [INR] in patients taking vitamin K antagonists,
- blood glucose levels in diabetic patients,
- immunosuppressive drug levels (e.g., calcineurin inhibitors cyclosporine and tacrolimus) in patients receiving immunosuppressive therapy,
- other relevant laboratory parameters in susceptible patients and/or other concomitant medications significantly affected by changes in hepatic function.

The dose of vitamin K antagonists, anti-diabetic agents, immunosuppressive agents, or other concomitant medications significantly affected by changes in hepatic function should be modified when necessary.

The effects of coadministered drugs on the exposure of sofosbuvir and GS-331007 are shown in Table 5. The effects of sofosbuvir on the exposure of coadministered drugs are shown in Table 6.

Table 5. Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[a]

Coadministered 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_{max}	AUC	C_{min}
Carbamazepine	300 twice daily	400 single dose	24	sofosbuvir	0.52 (0.43, 0.62)	0.52 (0.46, 0.59)	NA
				GS-331007	1.04 (0.97, 1.11)	0.99 (0.94, 1.04)	NA
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[b]	600 once daily	400 single dose	16	sofosbuvir	0.81 (0.60, 1.10)	0.94 (0.76, 1.16)	NA
Emtricitabine[b]	200 once daily						
Tenofovir disoproxil fumarate[c]	300 once daily			GS-331007	0.77 (0.70, 0.84)	0.84 (0.76, 0.92)	NA

Coadministered 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_{max}	AUC	C_{min}
Methadone	methadone maintenance therapy (30 to 130 daily)	400 once daily	14	sofosbuvir	0.95[c] (0.68, 1.33)	1.30[c] (1.00, 1.69)	NA
				GS-331007	0.73[c] (0.65, 0.83)	1.04[c] (0.89, 1.22)	NA
Raltegravir	400 twice daily	400 single dose	19	sofosbuvir	0.87 (0.71, 1.08)	0.95 (0.82, 1.09)	NA
				GS-331007	1.09 (0.99, 1.20)	1.03 (0.97, 1.08)	NA
Rifabutin	300 once daily	400 single dose	20	sofosbuvir	0.64 (0.53, 0.77)	0.76 (0.63, 0.91)	NA
				GS-331007	1.15 (1.03, 1.27)	1.03 (0.95, 1.12)	NA
Rifampin	600 once daily	400 single dose	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
				GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA
Rilpivirine	25 once daily	400 single dose	17	sofosbuvir	1.21 (0.90, 1.62)	1.09 (0.94, 1.27)	NA
				GS-331007	1.06 (0.99, 1.14)	1.01 (0.97, 1.04)	NA
Tacrolimus	5 single dose	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
				GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers

b. Administered as ATRIPLA®

c. Comparison based on historic control

Table 6. Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Sofosbuvir[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Coadministered Drug No Effect=1.00		
				C_{max}	AUC	C_{min}
Cyclosporine	600 single dose	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
Darunavir (boosted with ritonavir)	800/100 once daily	400 single dose	18	0.97 (0.94, 1.01)	0.97 (0.94, 1.00)	0.86 (0.78, 0.96)
Emtricitabine[b]	200 once daily	400 single dose	16	0.97 (0.88, 1.07)	0.99 (0.94, 1.05)	1.04 (0.98, 1.11)
Efavirenz[b]	600 once daily			0.95 (0.85, 1.06)	0.96 (0.91, 1.03)	0.96 (0.93, 0.98)
Tenofovir disoproxil fumarate[b]	300 once daily			1.25 (1.08, 1.45)	0.98 (0.91, 1.05)	0.99 (0.91, 1.07)
R-Methadone	Methadone maintenance therapy (30 to 130 mg/daily)	400 once daily	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone				0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)
Ethinyl estradiol	Norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily	400 once daily	15	1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Norgestrel				1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Norelgestromin				1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
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)
Rilpivirine	25 once daily	400 single dose	17	1.05 (0.97, 1.15)	1.06 (1.02, 1.09)	0.99 (0.94, 1.04)
Tacrolimus	5 single dose	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers.

b. Administered as ATRIPLA.

Drug-Food Interactions

Relative to fasting conditions, the administration of a single dose of SOVALDI with a standardized high fat meal slowed the rate of absorption of sofosbuvir but did not substantially affect the extent of absorption. The exposure (AUC) of the predominant circulating metabolite, GS-331007, was unaffected (90% CIs of the Geometric Mean Ratios

(GMRs) contained within 80-125%) by a high-fat meal, and although there was a modest decrease of 24% in C_{max} with a high-fat meal, the decrease was not considered clinically meaningful. Therefore, SOVALDI can be administered without regard to food (see **DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics** and **DETAILED PHARMACOLOGY**).

Drug-Herb Interactions

Coadministration of St. John's wort, a potent intestinal P-gp inducer, may decrease sofosbuvir plasma concentrations, which may result in loss of therapeutic effect.

St. John's wort should not be used with SOVALDI.

Drug-Laboratory Interactions

Interactions of SOVALDI with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

SOVALDI must only be used in combination with either pegylated interferon and ribavirin (genotypes 1 and 4, respectively), or ribavirin alone (genotypes 2 and 3, respectively).

Recommended Dose and Dosage Adjustment

The recommended dose of SOVALDI is one 400 mg tablet, taken orally, once daily with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

The recommended dose and treatment duration for SOVALDI combination therapy is provided in Table 7.

Table 7. Recommended Dose and Treatment Duration* for SOVALDI Combination Therapy in HCV Mono-infected and HIV-1 Co-infected Patients

	Duration	SOVALDI Dose (daily)	Peginterferon alfa Dose	Ribavirin Dose (daily)
Patients with genotype 1, or 4 CHC	12 weeks	400 mg	Refer to peginterferon alfa PM	Refer to PM containing ribavirin information
Patients with genotype 2 CHC	12 weeks		NA	<75 kg = 1000 mg[a] ≥75 kg = 1200 mg[a]
Patients with genotype 3 CHC	24 weeks			

NA = not applicable; PM = Product Monograph

* Treatment duration is fixed and is not guided by subjects' HCV RNA levels (ie, no response guided therapy).

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

SOVALDI in combination with ribavirin for 24 weeks can be considered as a therapeutic option for treatment naïve and non-cirrhotic treatment experienced CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen (See **CLINICAL TRIALS**). 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 (400 mg) in combination with weight-based ribavirin (< 75 kg = 1000 mg; or ≥ 75 kg = 1200 mg) is recommended for up to 48 weeks or until the time of liver transplantation, whichever occurs first, to prevent post-transplant HCV reinfection (see **CLINICAL TRIALS**).

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 accordingly or discontinued if necessary. If discontinuation is necessary, SOVALDI must also be discontinued (see **DOSAGE AND ADMINISTRATION**, **Discontinuation of Dosing**). Refer to the Product Monographs for peginterferon alfa and ribavirin 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 necessary, until the adverse reaction abates or decreases in severity. If discontinuation is necessary, SOVALDI must also be discontinued (see **DOSAGE AND ADMINISTRATION**, **Discontinuation of Dosing**). Table 8 provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

Table 8. Ribavirin Dose Modification Guideline for Coadministration with SOVALDI

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day[a] If:	Discontinue Ribavirin If:[b]
Hemoglobin in subjects with no cardiac disease	<10 g/dL	<8.5 g/dL
Hemoglobin in subjects with history of stable cardiac disease	≥2 g/dL decrease in hemoglobin during any 4 week treatment period	<12 g/dL despite 4 weeks at reduced dose

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

b Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1000 mg to 1200 mg daily).

Discontinuation of Dosing

If the pegylated interferon/ribavirin or ribavirin that is used in combination with SOVALDI is discontinued, SOVALDI must also be discontinued.

Pediatrics (<18 Years of age)

SOVALDI is not indicated for use in pediatric patients < 18 years of age.

Geriatrics (> 65 years of age)

No dose adjustment is warranted for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment

No dose adjustment of SOVALDI is required for patients with mild or moderate renal impairment. The safety and efficacy of SOVALDI has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). Refer also to ribavirin prescribing information for patients with CrCL <50 mL/min.

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 **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). Safety and efficacy of SOVALDI have not been established in patients with decompensated cirrhosis. See peginterferon alfa prescribing information for contraindication in hepatic decompensation.

Missed Dose

If a patient misses a dose of SOVALDI within the time it is usually taken, the patient should take SOVALDI as soon as possible, and then take the next dose of SOVALDI at the regularly scheduled time.

If a patient misses a dose of SOVALDI and it is almost time for the next dose, the patient should not take the missed dose, but resume the usual dosing schedule. A double dose of SOVALDI must not be taken.

If a patient vomits less than 2 hours after taking a dose of SOVALDI, the patient should take another dose of SOVALDI. If a patient vomits more than 2 hours after taking a dose of SOVALDI, the patient should take the next dose at the regularly scheduled time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. General supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient are recommended.

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

No specific antidote is available for overdose with SOVALDI. If overdose occurs the patient must be monitored for evidence of toxicity. Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. A 4-hour hemodialysis session removed 18% of the administered dose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Sofosbuvir is a DAA agent (pan-genotypic polymerase inhibitor) against the hepatitis C virus. HCV RNA replication is mediated by a membrane-associated multiprotein replication complex. The HCV polymerase (NS5B protein) is an RNA-dependent RNA polymerase (RdRp). It is the essential initiating and catalytic subunit of this replication complex and is critical for the viral replication cycle. There is no human homolog for HCV NS5B RdRp.

Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203). GS-461203 competes with natural nucleotides for incorporation (by HCV NS5B) into the nascent RNA strand during replication of the viral genome. GS-461203 differs from endogenous pyrimidine nucleotides in that it has been modified at the 2' position with the addition of a methyl and a fluoro functional group. Incorporation of GS-461203 into nascent RNA strongly reduces the efficiency of further RNA elongation by RdRp, resulting in premature termination of RNA synthesis. The stopping of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body.

Pharmacodynamics

Effect on Electrocardiogram

The electrocardiographic effects of sofosbuvir at the therapeutic dose (400mg) and 3-fold above therapeutic dose (1200 mg) were evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects. The trial demonstrated a lack of effect of sofosbuvir on prolongation of the QTcF interval. The upper bound of the two-sided 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern.

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 quickly and the peak plasma concentration was observed ~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.

Effects of Food

Relative to fasting conditions, the administration of a single dose of SOVALDI with a standardized high fat meal slowed the rate of absorption of sofosbuvir but did not

substantially affect the extent of absorption. 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 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of 14C-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 biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro.

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

Excretion:

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, 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. This data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-life of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

Special Populations and Conditions

Pediatrics:

The pharmacokinetics of sofosbuvir and GS-331007 in pediatric subjects have not been established.

Geriatrics:

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. Clinical studies of SOVALDI included 99 subjects (90

subjects received SOVALDI) 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.

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.

Hepatic Insufficiency:

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). 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 (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency:

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with end stage renal disease (ESRD) requiring hemodialysis following a single 400 mg dose of sofosbuvir. No dose adjustment is required for patients with mild or moderate renal impairment.

In subjects with severe renal impairment, the sofosbuvir and GS-331007 AUC_{inf} was 171% and 451% higher, respectively, compared to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2). In subjects with ESRD, sofosbuvir AUC_{inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The AUC_{inf} of GS-331007 in subjects with ESRD administered sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects.

Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. A 4 hour hemodialysis session removed approximately 18% of administered dose. The safety of SOVALDI has not been assessed in patients with severe renal impairment or ESRD (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and DETAILED PHARMACOLOGY**).

STORAGE AND STABILITY

Store at 15 to 30 °C (59 - 86 °F).

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

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

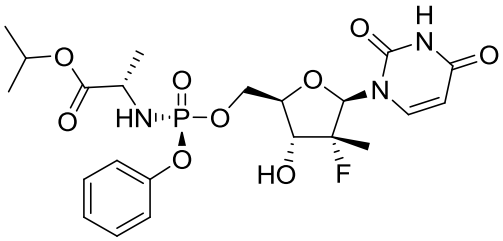
SOVALDI is available as tablets for oral administration. Each tablet contains 400 mg of sofosbuvir. The tablets include the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablets are film-coated with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

SOVALDI tablets are yellow, capsule-shaped, film-coated, debossed with “GSI” on one side and “7977” on the other side of the tablet. Each bottle contains 28 tablets, a silica gel desiccant, polyester coil and closed with a child resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	sofosbuvir
Chemical name:	(*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate
Molecular formula:	$C_{22}H_{29}FN_3O_9P$
Molecular mass:	529.45
Structural formula:	
Physicochemical properties:	Sofosbuvir is a white to off-white crystalline solid and is slightly soluble in water.

CLINICAL TRIALS

The 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), one Phase 3 trial in 223 HIV-1 co-infected subjects with genotype 1,2 or 3 CHC and one Phase 2 trial in 61 subjects with genotype 1 through 6 HCV infection and hepatocellular carcinoma (HCC) meeting the Milan criteria awaiting liver transplantation. One of the five trials 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 trials 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 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. Peginterferon (Peg-IFN) alfa 2a dose was 180 micrograms per week and the ribavirin (RBV) dose was weight-based 1000-1200 mg daily administered in two divided doses when used in combination with SOVALDI. 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 quantitation (LLOQ) of 25 IU per mL. Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate for all trials which was defined as HCV RNA less than 25 IU per mL at 12 weeks after the end of treatment.

Clinical Trials in Subjects with Genotype 1 or 4 Chronic Hepatitis C

Treatment-Naïve Subjects – NEUTRINO (Study 110)

Study demographics and trial design

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.

Demographic characteristics for subjects in NEUTRINO are provided in Table 9.

Table 9. Study Treatment and Demographic Characteristics of Adult Subjects in NEUTRINO

Study	Dosage, Route of Administration and Duration	Demographics Total
NEUTRINO	**SOVALDI 400 mg once daily p.o. + PEG-IFN alfa 180 µg/week s.c. + RBV 1000 or 1200 mg/day p.o., 12 weeks**	**N = 327** **Gender: n (%)** Male – 209 (64%) Female – 118 (36%) **Age: median (range)** 54 (19–70) **Race: n (%)** White – 257 (79) Black – 54 (17) Asian – 7 (2) Other – 8 (2) Missing – 1 **Body Mass Index: mean (range)** 29 kg/m^2 (18-56 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 256 (78)

Study	Dosage, Route of Administration and Duration	Demographics Total
		Cirrhosis: n (%) Yes – 54 (17%) **HCV Genotype: n (%)** Genotype 1 – 292 (89) Genotype 4 – 28 (9) Genotype 5 or 6 – 7 (2)

Study Results

Table 10 presents the response rates for the treatment group of SOVALDI + peginterferon alfa + ribavirin.

Table 10. Virologic Outcome in Study NEUTRINO

	SOVALDI + Peg-IFN alfa + RBV 12 weeks
	N=327
Overall SVR	90% (295/327)
<LLOQ[a] at treatment week 12	100% (327/327)
Outcome for subjects without SVR	
On-treatment virologic failure	0/327
Relapse[b]	9% (28/326)
Other[c]	1% (4/327)
Death[d]	0/327
Discontinued study treatment due to adverse event (AE)	2% (5/327)
Discontinued study treatment for other reasons	<1% (2/327)

a. Number of subjects reporting HCV RNA < LLOQ (Lower Limit of Quantitation) detected + the number of subjects with HCV RNA < LLOQ TND (target not detected).

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 (eg, lost to follow-up).

d. Treatment emergent death.

Response rates for selected subgroups are presented in Table 11.

Table 11. SVR Rates for Selected Subgroups in NEUTRINO

	SOVALDI + Peg-IFN alfa + RBV 12 weeks
Genotype	
Genotype 1[a]	89% (261/292)
Genotype 1a	92% (206/225)
Genotype 1b	82% (54/66)
Genotype 4	96% (27/28)
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)

a One subject had genotype 1a/1b mixed infection.

SVR rates were similarly high in subjects with baseline IL28B C/C allele [93/95 (98%)] and non-C/C (C/T or T/T) allele [202/232 (87%)].

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 11). 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).

Clinical Trials in Subjects with Genotype 2 or 3 Chronic Hepatitis C

Treatment Naïve Adults – FISSION (Study 1231)

Study demographics and trial design

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_{10}IU/mL vs ≥ 6 log_{10}IU/mL). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio.

Table 12. Study Treatment and Demographic Characteristics of Adult Subjects in FISSION

Study	Dosage, Route of Administration and Duration	Demographics Treatment Arm	Comparator	Total
FISSION	**SOVALDI 400 mg p.o. + RBV 1000-1200 mg p.o. daily; 12 weeks (Treatment Arm)** **PEG-IFN 180 µg/week + RBV 800 mg/day; 24 weeks (Comparator Arm)**	**N = 256** **Gender: n (%)** Male 171 (67%) Female 85 (33%) **Age: median (range)** 50 (20-72) **Race: n (%)** White – 223 (87) Black – 12 (5) Asian – 14 (6) Other – 7 (3) **Body Mass Index: mean (range)** 28 kg/m^2 (17-51 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 log_{10} IU/mL – 148 (58) **Cirrhosis: n (%)** Yes – 50 (20%) **HCV Genotype: n (%)** Genotype 1 – 3 (1) Genotype 2 – 70 (27) Genotype 3 – 183 (72)	**N = 243** **Gender: n (%)** Male 156 (64%) Female 87 (36%) **Age: median (range)** 50 (19-77) **Race: n (%)** White – 212 (87) Black – 5 (2) Asian – 15 (6) Other – 11 (5) **Body Mass Index: mean (range)** 28 kg/m^2 (19-52 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 log_{10} IU/mL – 137 (56) **Cirrhosis: n (%)** Yes – 50 (20%) **HCV Genotype: n (%)** Genotype 1 – 0 Genotype 2 – 67 (28) Genotype 3 – 176 (72)	**N = 499** **Gender: n (%)** Male 327 (66%) Female 172 (34%) **Age: median (range)** 50 (19–77) **Race: n (%)** White – 435 (87) Black – 17 (3) Asian – 29 (6) Other – 18 (4) **Body Mass Index: mean (range)** 28 kg/m^2 (17-52 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 log_{10} IU/mL – 285 (57) **Cirrhosis: n (%)** Yes – 100 (20%) **HCV Genotype: n (%)** Genotype 1 – 3 (1) Genotype 2 – 137 (27) Genotype 3 – 359 (72)

Study Results

Table 13 presents the response rates for the treatment groups of SOVALDI + ribavirin and peginterferon alfa + ribavirin.

Table 13. Virologic Outcome in Study FISSION

	SOVALDI + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	N=256[a]	N=243[a]
Overall SVR	67% (171/256)	67% (162/243)
Genotype 2	95% (69/73)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
<LLOQ[b] at treatment week 12	99% (245/247)	92% (207/224)
Outcome for subjects without SVR		
On-treatment virologic failure	<1% (1/256)	7% (18/243)
Relapse[c]	30% (76/252)	21% (46/217)
Other[d]	3% (8/256)	7% (17/243)
Death[e]	<1% (1/256)	0/243
Discontinued study treatment due to adverse event (AE)	1% (3/256)	11% (26/243)
Discontinued study treatment for other reasons	3% (17/256)	12% (28/243)

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

b. Number of subjects reporting HCV RNA < LLOQ (Lower Limit of Quantitation) detected + the number of subjects with HCV RNA < LLOQ TND (target not detected).

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 (eg, lost to follow-up).

e. Treatment emergent death.

The difference in the overall SVR rates between SOVALDI + ribavirin and peginterferon alfa + ribavirin treatment groups was 0.3% (95% confidence interval: -7.5% to 8.0%) and the study met the predefined noninferiority criterion.

Among the small number of Black/African Americans enrolled in the trial, 75% (9/12) subjects achieved SVR in the SOVALDI + ribavirin treatment group compared to 40% (2/5) in the peginterferon alfa + ribavirin treatment group.

Response rates for subjects with cirrhosis at baseline are presented in Table 14 by genotype.

Table 14. 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)

Study demographics and trial design

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).

Table 15. Study Treatment and Demographic Characteristics of Adult Subjects in POSITRON

Study	Dosage, Route of Administration and Duration	Demographics Treatment Arm	Comparator Arm	Total
POSITRON	**SOVALDI 400 mg p.o. + RBV 1000-1200 mg p.o. daily; 12 weeks (Treatment Arm)** **Placebo; 12 weeks (Comparator Arm)**	**N = 207** **Gender: n (%)** Male 117 (57%) Female 90 (44%) **Age: median (range)** 53 (21–75) **Race: n (%)** White – 188 (91) Black – 9 (4) Asian – 7 (3) Other – 3 (1) **Body Mass Index: mean (range)** 28 kg/m^2 (18-53 kg/m^2) **Baseline HCV RNA Category: n (%)**	**N = 71** **Gender: n (%)** Male 34 (48%) Female 37 (52%) **Age: median (range)** 54 (28–67) **Race: n (%)** White – 66 (93) Black – 4(6) Asian – 1 (1) Other – 0 **Body Mass Index: mean (range)** 28 kg/m^2 (20-43 kg/m^2) **Baseline HCV RNA Category: n (%)**	**N = 278** **Gender: n (%)** Male 151 (54%) Female 127 (46%) **Age: median (range)** 54 (21-75) **Race: n (%)** White – 254 (91) Black – 13 (5) Asian – 8 (3) Other – 3 (1) **Body Mass Index: mean (range)** 28 kg/m^2 (18-53 kg/m^2) **Baseline HCV RNA Category: n (%)**

Study	Dosage, Route of Administration and Duration	Demographics Treatment Arm	Comparator Arm	Total
		≥ 6 $\log_{10}$ IU/mL – 140 (68) **Cirrhosis: n (%)** Yes – 31 (15%) **HCV Genotype: n (%)** Genotype 2 – 109 (53) Genotype 3 – 98 (47) **Interferon Classification: n (%)** Ineligible – 88 (43) Intolerant – 17 (8) Unwilling – 102 (49) **Prior HCV Treatment: n (%)** No – 170 (82)	≥ 6 $\log_{10}$ IU/mL – 54 (76) **Cirrhosis: n (%)** Yes – 13 (18%) **HCV Genotype: n (%)** Genotype 2 – 34 (48) Genotype 3 – 37 (52) **Interferon Classification: n (%)** Ineligible – 33 (47) Intolerant – 8 (11) Unwilling – 30 (42) **Prior HCV Treatment: n (%)** No – 56 (79)	≥ 6 $\log_{10}$ IU/mL – 194 (70) **Cirrhosis: n (%)** Yes – 44 (16%) **HCV Genotype: n (%)** Genotype 2 – 143 (51) Genotype 3 – 135 (49) **Interferon Classification: n (%)** Ineligible – 121 (44) Intolerant – 25 (9) Unwilling – 132 (47) **Prior HCV Treatment: n (%)** No – 226 (81)

Table 16 presents the response rates for the treatment groups of SOVALDI + ribavirin and placebo.

Table 16. Virologic Outcome in Study POSITRON

	SOVALDI + RBV 12 weeks N=207	Placebo 12 weeks N=71
Overall SVR	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
<LLOQ[a] at treatment week 12	100% (202/202)	0/68
Outcome for subjects without SVR		
On-treatment virologic failure	0/207	97% (69/71)
Relapse[b]	20% (42/205)	0/0
Other[c]	2% (4/207)	3% (2/71)
Death[d]	0/207	0/71
Discontinued study treatment due to adverse event (AE)	2% (4/207)	4% (3/71)
Discontinued study treatment for other reasons	<1% (2/207)	0% (0/71)

a. Number of subjects reporting HCV RNA < LLOQ (Lower Limit of Quantitation) detected + the number of subjects with HCV RNA < LLOQ TND (target not detected).
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 (eg, lost to follow-up).
d. Treatment emergent death.

The SVR12 rate in the SOVALDI + ribavirin treatment group was statistically significant when compared to placebo ($p < 0.001$).

Table 17 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 17. 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)

Study demographics and trial design

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).

Table 18. Study Treatment and Demographic Characteristics of Adult Subjects in FUSION

Study	Dosage	Demographics Treatment Arm 1	Treatment Arm 2	Total
FUSION	**SOVALDI 400 mg p.o. + RBV 1000 or 1200 mg p.o. daily; 12 weeks (Treatment Arm 1)** **SOVALDI 400 mg p.o. + RBV 1000 or 1200 mg p.o. daily; 16 weeks (Treatment Arm 2)**	**N = 103** **Gender: n (%)** Male 73 (71%) Female 30 (29%) **Age: median (range)** 56 (30-69) **Race:** White – 88 (85) Black – 5 (5) Asian – 7 (7) Other – 3 (3) Missing – 0 **Body Mass Index: mean (range)** 28 kg/m^2 (19-43 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 77 (75) **Cirrhosis: n (%)** Yes – 36 (35%) **HCV Genotype: n (%)** Genotype 1 – 3 (3) Genotype 2 – 36 (35) Genotype 3 – 64 (62) **Response to Prior HCV Treatment: n (%)** Relapser – 78 (76)	**N = 98** **Gender: n (%)** Male 67 (68%) Female 31 (31%) **Age: median (range)** 55 (24-70) **Race:** White – 86 (88) Black – 1 (1) Asian – 5 (5) Other – 6 (6) Missing – 1 (1) **Body Mass Index: mean (range)** 29 kg/m^2 (20-44 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 69 (70) **Cirrhosis: n (%)** Yes – 32 (33%) **HCV Genotype: n (%)** Genotype 1 – 3 (3) Genotype 2 – 32 (33) Genotype 3 – 63 (64) **Response to Prior HCV Treatment: n (%)** Relapser – 73 (75)	**N = 201** **Gender: n (%)** Male 140 (70%) Female 61 (30%) **Age: median (range)** 56 (24–70) **Race:** White – 174 (87) Black – 6 (3) Asian – 12 (6) Other – 9 (4) Missing – 1 (0.5) **Body Mass Index: mean (range)** 29 kg/m^2 (19-44 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 146 (73) **Cirrhosis: n (%)** Yes – 68 (34%) **HCV Genotype: n (%)** Genotype 1 – 6 (3) Genotype 2 – 68 (34) Genotype 3 – 127 (63) **Response to Prior HCV Treatment: n (%)** Relapser – 151 (75)

Table 19 presents the response rates for the treatment groups of SOVALDI + ribavirin for 12 weeks and 16 weeks.

Table 19. Virologic Outcome in Study FUSION

	SOVALDI + RBV 12 weeks	**SOVALDI + RBV 16 weeks**
	N= 103[a]	N=98[a]
Overall SVR	50% (51/103)	71% (70/98)
Genotype 2	82% (32/39)	89% (31/35)
Genotype 3	30% (19/64)	62% (39/63)
<LLOQ[b] at treatment week 12	100% (103/103)	100% (98/98)
<LLOQ[b] at treatment week 16	Not Applicable	100% (98/98)
Outcome for subjects without SVR		
On-treatment virologic failure	0/103	0/98
Relapse[c]	48% (49/103)	29% (28/98)
Other[d]	3% (3/103)	0/98
Death[e]	0/103	0/98
Discontinued study treatment due to adverse event (AE)	1% (1/103)	0/98
Discontinued study treatment for other reasons	0% (0/103)	0% (0/103)

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

b. Number of subjects reporting HCV RNA < LLOQ (Lower Limit of Quantitation) detected + the number of subjects with HCV RNA < LLOQ TND (target not detected).

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 (eg, lost to follow-up)

e. Treatment emergent death.

Table 20 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

Table 20. 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	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)

Study demographics and trial design

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.

Table 21. Study Treatment and Demographic Characteristics of Adult Subjects in VALENCE

	Demographics*			
Study	**Genotype 2 SOVALDI + RBV** 12 Weeks**	**Genotype 3 SOVALDI + RBV** 24 Weeks**	**SOVALDI Placebo + RBV Placebo****	**Total**
VALENCE	**N = 73** **Gender: n (%)** Male - 40 (55) Female - 33 (45) **Age: median (range)** 60 (28–74) **Race: n (%)** White – 65 (89) Black – 5 (7) Asian – 1 (1) Not permitted – 2 (3) **Body Mass Index: mean (range)** 26 kg/m^2 (20-35 kg/m^2) **Baseline HCV RNA: median (range)** 6.7 $\log_{10}$ IU/mL (4.6-7.6) **Cirrhosis: n (%)** Yes – 10 (14) **Prior HCV Treatment Experience And Interferon Classification: n (%)** *Experienced - 41 (56)* IFN Intolerant - 3 (7) Non-Response - 10 (24) Relapse/Breakthrough - 28 (68) *Naïve - 32 (44)* IFN-eligible - 27 (84) IFN-ineligible - 5 (16)	**N = 250** **Gender: n (%)** Male - 155 (62) Female - 95 (38) **Age: median (range)** 50 (19–69) **Race: n (%)** White – 236 (94) Black – 0 Asian – 9 (4) Not permitted – 5 (2) **Body Mass Index: mean (range)** 25 kg/m^2 (17-41 kg/m^2) **Baseline HCV RNA: median (range)** 6.5 $\log_{10}$ IU/mL (3.5-7.6) **Cirrhosis: n (%)** Yes – 58 (23) **Prior HCV Treatment Experience And Interferon Classification: n (%)** *Experienced - 145 (58)* IFN Intolerant - 10 (7) Non-Response - 41 (28) Relapse/Breakthrough - 94 (65) *Naïve - 105 (42)* IFN-eligible - 94 (90) IFN-ineligible - 11 (10)	**N = 85** **Gender: n (%)** Male - 49 (58) Female - 36 (42) **Age: median (range)** 51 (19–72) **Race: n (%)** White – 81 (95) Black – 1 (1) Asian – 3 (4) Not permitted – 0 **Body Mass Index: mean (range)** 25 kg/m^2 (18-40 kg/m^2) **Baseline HCV RNA: median (range)** 6.7 $\log_{10}$ IU/mL (4.6-7.4) **Cirrhosis: n (%)** Yes – 18 (21) **Prior HCV Treatment Experience And Interferon Classification: n (%)** *Experienced - 50 (59)* IFN Intolerant - 0 Non-Response - 18 (36) Relapse/Breakthrough - 32 (64) *Naïve - 35 (41)* IFN-eligible - 30 (86) IFN-ineligible - 5 (14)	**N = 419** **Gender: n (%)** Male - 250 (60) Female - 169 (40) **Age: median (range)** 51 (19–74) **Race: n (%)** White – 393 (94) Black – 6 (1) Asian – 13 (3) Not permitted – 7 (2) **Body Mass Index: mean (range)** 25 kg/m^2 (17-44 kg/m^2) **Baseline HCV RNA: median (range)** 6.6 $\log_{10}$ IU/mL (3.5-7.6) **Cirrhosis: n (%)** Yes – 88 (21) **Prior HCV Treatment Experience And Interferon Classification: n (%)** *Experienced - 245 (58)* IFN Intolerant - 13 (5) Non-Response - 73 (30) Relapse/Breakthrough - 159 (65) *Naïve - 174 (42)* IFN-eligible - 153 (88) IFN-ineligible - 21 (12)

*Demographics for GT3 patients receiving 12 weeks (N=11) were similar.
**Dosage: SOVALDI 400 mg p.o. daily, RBV 1000 or 1200 mg p.o. daily

Table 22 presents the response rates for the treatment groups of SOVALDI + ribavirin for 12 weeks (Genotype 2) and 24 weeks (Genotype 3). Eleven genotype 3 subjects who received SOVALDI + ribavirin for 12 weeks had an overall SVR12 rate of 27.3%. Placebo subjects (N=85) are not included in the table as none achieved SVR12.

Table 22. Virologic Outcome in Study VALENCE

	Genotype 2 SOVALDI + RBV 12 weeks	**Genotype 3 SOVALDI + RBV 24 weeks**
	N=73	N=250[a]
Overall SVR	93% (68/73)	84% (210/250)
Outcome for subjects without SVR		
On-treatment virologic failure	0% (0/73)	<1% (1/250)
Relapse[b]	7% (5/73)	14% (34/249)
Treatment-naïve	3% (1/32)	5% (5/105)
Treatment-experienced	10% (4/41)	20% (29/144)
Other[c]	0% (0/73)	2% (5/250)
Death[d]	0/73	0/250
Discontinued study treatment due to adverse event (AE)	0/73	<1% (1/250)
Discontinued study treatment for other reasons	0/73	1% (3/250)

a. Eleven genotype 3 subjects who received SOVALDI + ribavirin for 12 weeks were not included.
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 SVR12 and did not meet virologic failure criteria (eg, lost to follow up).
d. Treatment emergent death.

Table 23 presents the subgroup analysis by genotype for cirrhosis and prior HCV treatment experience.

Table 23. SVR Rates for Selected Subgroup by Genotype in Study VALENCE

	Genotype 2 SOVALDI + RBV 12 weeks	**Genotype 3 SOVALDI + RBV 24 weeks**
	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)

Clinical Trials in Special Populations

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. Subjects were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm^3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm^3.

Table 24. Study Treatment and Demographic Characteristics of Adult Subjects in PHOTON-1

	Demographics					
Characteristics	**GT1 TN SOVALDI + RBV* 24 weeks[a] N = 114**	**GT2 TN SOVALDI + RBV* 12 weeks[a] N = 26**	**GT2 TE SOVALDI + RBV* 24 weeks[a] N = 24**	**GT3 TN SOVALDI + RBV* 12 weeks[a] N = 42**	**GT3 TE SOVALDI + RBV* 24 weeks[a] N = 17**	**Total N = 223**
Gender: n (%)						
Male	93 (82)	21 (81)	23 (96)	34 (81)	14 (82)	185 (83)
Female	21 (18)	5 (19)	1 (4)	8 (19)	3 (18)	38 (17)
Age: median (range)	49 (25-70)	51 (24-69)	54 (42-68)	49 (28-71)	54 (34-65)	51 (24–71)
Race:						
White	69 (61)	17 (65)	17 (71)	35 (83)	15 (88)	153 (69)
Black	37 (32)	6 (23)	6 (25)	2 (5)	1 (6)	52 (23)
Asian	1 (1)	0	1 (4)	1 (2)	0	3 (1)
Other	7 (6)	3 (12)	0	4 (10)	1 (6)	9 (4)
Body Mass Index: mean (range) kg/m^2	27 (19-46)	27 (21-32)	29 (19-40)	28 (20-44)	26 (22-33)	27 (19-46)
Baseline HCV RNA Category: n (%)						
≥ 6 $\log_{10}$ IU/mL	92 (81)	20 (77)	19 (79)	27 (64)	15 (88)	173 (78)
Cirrhosis: n (%)						
Yes	5 (4)	1 (4)	4 (17)	6 (14)	6 (35)	22 (10)
HCV Genotype: n (%)						
Genotype 1	114 (100)	0	0	0	0	114 (51)
Genotype 2	0	26 (100)	24 (100)	0	0	50 (22)
Genotype 3	0	0	0	42 (100)	17 (100)	59 (27)
IL28B Genotype:						

Characteristics	Demographics					
	GT1 TN SOVALDI + RBV* 24 weeks[a] N = 114	**GT2 TN SOVALDI + RBV* 12 weeks[a] N = 26**	**GT2 TE SOVALDI + RBV* 24 weeks[a] N = 24**	**GT3 TN SOVALDI + RBV* 12 weeks[a] N = 42**	**GT3 TE SOVALDI + RBV* 24 weeks[a] N = 17**	**Total N = 223**
n (%)						
CC	30 (27)	10 (39)	10 (42)	15 (36)	10 (59)	75 (34)
non-CC	83 (73)	16 (61)	14 (58)	27 (64)	7 (41)	147 (66)
Missing	1 (<1)	0	0	0	0	1 (<1)
On ARV Treatment at Enrollment: n (%)						
Yes	112 (98)	22 (85)	23 (96)	39 (93)	16 (94)	212 (95)

*Dosage: SOVALDI 400 mg p.o. daily, RBV 1000 or 1200 mg p.o. daily

a Treatment duration based upon genotype and prior treatment history.

Note: Genotype 2 and 3 subjects were either HCV treatment naïve or treatment experienced whereas genotype 1 subjects were all treatment naïve.

Efficacy data 12 weeks post treatment are available for 210 subjects (see Table 25).

Table 25. Virologic Outcome in Study PHOTON-1[a]

	HCV genotype 1	HCV genotype 2	HCV genotype 3
	SOVALDI + RBV 24 weeks TN (N=114)	SOVALDI + RBV 12 weeks TN (N=26)	SOVALDI + RBV 24 weeks TE (N=13)
Overall	76% (87/114)	88% (23/26)[a]	92% (12/13)
Outcome for subjects without SVR12			
On-treatment virologic failure	1% (1/114)	4% (1/26)	0/13
Relapse[b]	22% (25/113)	0/25	8% (1/13)
Other[c]	1% (1/114)	8% (2/26)	0/13
Death[d]	0/114	0/26	0/13
Discontinued study treatment due to adverse event (AE)	3% (3/114)	4% (1/26)	0/13
Discontinued study treatment for other reasons	7% (8/114)	8% (2/26)	0/13

TN = Treatment-naïve; TE = Treatment-experienced

a. 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) achieved overall SVR12 rates of 93 % and 67% respectively. These subjects are not included in the table.

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 SVR12 and did not meet virologic failure criteria (eg, lost to follow up).

d. Treatment emergent death

In the 223 CHC subjects with HIV-1 co-infection, the CD4+ cell percentage did not change during treatment. Median CD4+ cell count decreases of 85 cells/mm^3 and 84 cells/mm^3 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.

Table 26. SVR Rates for Selected Subgroups in Study PHOTON-1

	SOVALDI + RBV 24 weeks GT1 TN	SOVALDI + RBV 12 weeks GT2/3 TN	SOVALDI + RBV 24 weeks GT2/3 TE
	N=114	N=68	N = 28
HCV Genotype			
Genotype 1a	82% (74/90)	N/A	N/A
Genotype 1b	54% (13/24)	N/A	N/A
Genotype 2	N/A	86% (23/26)	93% (14/15)
Genotype 3	N/A	67% (28/42)	92% (12/13)
IL28B Genotype			

CC	68% (17/25)	92% (11/12)	80% (24/30)
Non-CC	79% (34/43)	94% (15/16)	75% (62/83)

Patients Awaiting Liver Transplantation:

SOVALDI was studied in HCV-infected subjects 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) (HCV RNA < lower limit of quantitation [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 1000-1200 mg ribavirin daily for up to 48 weeks or until the time of liver transplantation, whichever occurred first.

Demographics and baseline disease characteristics are presented in Table 27.

Table 27. Study Treatment and Demographic Characteristics of Adult Subjects in P7977-2025

Study	Dosage	Demographics
P7977-2025	**SOVALDI 400 mg p.o. + RBV 1000 or 1200 mg p.o. daily; up to 48 weeks or until liver transplant**	**N = 61** **Gender: n (%)** Male - 49 (80%) Female - 12 (20%) **Age: median (range)** 59 (46–73) **Race:** White – 55 (90) Black – 6 (10) **Body Mass Index: mean (range)** 28 kg/m^2 (20-59 kg/m^2) **Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 41 (67) **HCV Genotype: n (%)** Genotype 1a – 24 (39) Genotype 1b – 21 (34) Genotype 2a – 1 (2) Genotype 2b – 7 (12) Genotype 3a – 7 (12) Genotype 4a – 1 (2)

Study	Dosage	Demographics
		IL28B Genotyp: n (%) CC – 13 (22) non-CC – 48 (78) **Prior HCV Treatment: n (%)** Yes – 46 (75)

An interim analysis was conducted on 61 subjects who received SOVALDI and ribavirin; 45 subjects had HCV genotype 1; 44 subjects had a baseline Child-Pugh-Turcotte score less than 7 and all subjects had a baseline unadjusted MELD score ≤14. Virologic outcomes are presented in Table 28. Duration of viral suppression prior to transplantation was the most predictive factor for pTVR in those who were HCV RNA <LLOQ at the time of transplantation.

Table 28. Virologic Outcome in Study P7977-2025

	SOVALDI + RBV N = 61
Number of Subjects Transplanted	44
Number of Subjects with HCV RNA <LLOQ at time of transplantation	41
pTVR rate at Posttransplant Week 12	62% (23/37)[a]

pTVR: post-transplant virologic response

a Of the 41 subjects with HCV RNA <LLOQ at time of transplantation, there were 37 evaluable subjects who reached the 12 week post-transplant time point.

DETAILED PHARMACOLOGY

Pharmacodynamics

Effect on Electrocardiogram

The recommended therapeutic dose (400 mg) and 3-fold above the recommended therapeutic dose (1200 mg) of sofosbuvir were evaluated for effect on the QTc interval when administered to healthy subjects. Administration of a 1200-mg dose provided C_{max} increases of approximately 3.6- and 1.9-fold and AUC_{inf} increases of approximately 3.9- and 2.5-fold for sofosbuvir and GS-331007, respectively, when compared to 400 mg. The results from this study showed the expected effect of the single dose of moxifloxacin (positive control) on the QTc interval (QTcF, QTcB, QTcN, and QTcI), indicating that the study had appropriate assay sensitivity; the lower bound of the 2-sided 90% confidence interval was > 5 msec at more than 1 time point.

Evaluation of the baseline-adjusted mean differences between sofosbuvir 400 mg or 1200-mg doses and placebo and their associated 2-sided 90% confidence intervals demonstrated a lack of effect of sofosbuvir on prolongation of the QTcF interval (primary PD endpoint). The

upper bounds of the 90% confidence intervals were < 10 msec at all time points after dosing. Consistent with the results using the QTcF correction formula, the upper bounds of the 2-sided 90% confidence intervals were < 10 msec for both sofosbuvir doses at all time points using other correction methods.

The mean exposure of GS-331007 (AUC_{tau} and C_{max}) and sofosbuvir (AUC_{tau}) at the sofosbuvir 1200 mg dose was 3.8-, 3.6-, and 2.9-fold higher, respectively, than the mean exposure (based on population PK exposures) achieved in Phase 3 studies, and indicated adequate QTc safety margins for GS-331007 and sofosbuvir in the event of overdose or a drug-drug interaction.

Safety Pharmacology

The effects of sofosbuvir (evaluated as GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer) on the central nervous, cardiovascular, and respiratory systems were examined in a core battery of safety pharmacology studies. The studies presented have not identified any undesirable pharmacodynamic effect of sofosbuvir on physiological function at therapeutic dose level.

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 quickly and the peak plasma concentration was observed ~0.5-2 hour post-dose, regardless of dose level in healthy subjects or HCV-infected subjects. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose. The absolute bioavailability of sofosbuvir was not specifically evaluated; however, at least 80% of an administered dose was absorbed into systemic circulation based upon urinary recovery (measured by LC/MS/MS). 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} and C_{max} were 969 ng•hr/mL and 479 ng/mL for sofosbuvir (N=838), and 6790 ng•hr/mL and 543 ng/mL for GS-331007 (N=1695), respectively. Relative to healthy subjects administered sofosbuvir alone (N = 272), the sofosbuvir AUC_{0-24} and C_{max} were 60% higher and 39% higher; and GS-331007 AUC_{0-24} and C_{max} were 39% lower and 50% 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.

Effects of Food

A study conducted in 39 healthy subjects, showed that relative to fasting conditions, the administration of a single dose of SOVALDI with a standardized high fat meal slowed the rate of absorption of sofosbuvir (high-fat meal versus fasted; prolonged T_{max}: 1.5 versus 0.5 hours) but did not substantially affect the extent of absorption. When evaluated as GS-331007, prolonged T_{max} (high-fat meal vs fasted; 4.00 vs 2.00 hours) and modestly lower

C_{max} (high-fat meal vs fasted; Geometric Least Squares Mean (GLSM) ratio for C_{max} 24% decreased) were observed. $AUC_{0\text{-last}}$ and AUC_{inf} of GS-331007 were unaltered in the presence of a high-fat meal. The decrease in C_{max} was not considered clinically significant and 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 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy male subjects (n=7), the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

[^{14}C]-sofosbuvir-derived radioactivity was absorbed and widely distributed to tissues (eg, alimentary canal, lymphatic system, excretory system) of male rats and pregnant, non-pregnant, and postpartum female rats after a single oral dose. Drug-derived radioactivity was transferred through the placenta of females and was found in amniotic fluid and absorbed into fetuses. Fetal blood and brain levels of drug-related material were higher than those observed in dams. Levels of drug-derived radioactivity were quantifiable in the milk collected from postpartum females (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Nursing Women**). Levels of drug-derived radioactivity were transferred into nursing pups and were detectable in the liver and gastrointestinal (GI)/stomach contents.

Metabolism

The metabolism of sofosbuvir, including metabolic routes leading to elimination and activation, was characterized in vitro (in plasma, blood, various hepatic-derived extracts, cells, and enzyme preparations) and in a human mass balance PK study.
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 biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro.

After a single 400 mg oral dose of [^{14}C]-sofosbuvir in healthy male subjects (n=7), sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

Excretion

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir in healthy male subjects (n=7), 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. Renal clearance is the major elimination pathway for GS-331007. Consistent with substantial elimination of GS-331007 in the urine, clinically significant changes in GS-331007 PK were noted with declining renal function. The median terminal half-life of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

Special Populations and Conditions

Hepatic Insufficiency:

The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 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 (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency:

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with end stage renal disease (ESRD) requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD, sofosbuvir AUC_{inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The AUC_{inf} of GS-331007 in subjects with ESRD administered SOVALDI 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects.

Hemodialysis is required for the elimination of GS-331007 (extraction ratio 53%) in subjects with ESRD, with a 4 hour hemodialysis removing approximately 18% of administered dose. No dose adjustment is required for patients with mild or moderate renal impairment. The safety of SOVALDI has not been assessed in patients with severe renal impairment or ESRD (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions

In vitro studies indicated that sofosbuvir and GS-331007 are not inhibitors of human CYP isozymes CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2C8, and CYP2D6 or UGT1A1. Sofosbuvir caused little to no induction of CYP enzymes. Sofosbuvir and GS-331007 were minimally metabolized by FMO, UGT, or CYP. Sofosbuvir and GS-331007 showed little or no inhibition of Pgp, BCRP, OATP1B1, OATP1B3, OCT1, and BSEP. GS-331007 showed little or no inhibition of the renal transporters OAT1, OAT3, OCT2, and MATE1.

Sofosbuvir is a substrate for Pgp and BCRP but not OCT1, OATP1B1, or OATP1B3. GS-331007 is not a substrate for Pgp, BCRP or the renal transporters OAT1, OAT3, OCT2, and MATE1.

Based on these data sofosbuvir and its metabolites are predicted to have low liability to cause clinically significant drug interactions through human CYP or drug transporters. Sofosbuvir and its metabolites are predicted to have low liability to be affected by enzyme-mediated drug interactions. The fact that sofosbuvir is a substrate of Pgp and BCRP suggests that sofosbuvir may be susceptible to modest changes in PK that can occur via Pgp and/or BCRP transporter-based drug interactions. Clinical studies were conducted to evaluate the effect of drugs that can affect or be affected by sofosbuvir and GS-331007 during co-administration (see **DRUG INTERACTIONS)**.

MICROBIOLOGY

Antiviral Activity

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

Since there is about 65% homology of the HCV NS5B polymerase across HCV genotypes, and since GS-461203 binds to a highly conserved region of RdRp, sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B polymerase with a high barrier to resistance. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with an IC50 value 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.

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. 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, the ability of the active triphosphate of sofosbuvir (GS-461203) to inhibit recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution was reduced compared to its ability to inhibit wild-type recombinant NS5B polymerase, as indicated by a 8-24-fold increase in IC_{50}.

In Clinical Trials

In a pooled analysis of 991 subjects who received SOVALDI in Phase 3 trials (NEUTRINO, FISSION, POSITRON and FUSION), 226 subjects qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA > 1000 IU/ml. Post-baseline NS5B sequences were available for 225 of the 226 subjects, with deep sequencing data (assay cutoff of 1%) from 221 of these subjects. The sofosbuvir-associated resistance substitution S282T was not detected in any of these subjects by deep sequencing or population sequencing. No other NS5B substitutions were identified to be associated with resistance to sofosbuvir by deep sequencing and phenotypic analyses. The S282T substitution in NS5B was detected in a single subject receiving SOVALDI monotherapy in a Phase 2 trial. This subject harbored <1% S282T at baseline and developed S282T (>99%) at 4 weeks post-treatment which resulted in a 14-fold change in sofosbuvir EC50 and reduced viral replication capacity. The S282T substitution reverted to wild-type over the next 8 weeks and was no longer detectable by deep sequencing at 12 weeks post-treatment.

Effect of Baseline HCV Polymorphisms on Treatment Outcome

Baseline NS5B sequences were obtained for 1292 subjects from Phase 3 trials by population sequencing and the S282T substitution was not detected in any subject with available baseline sequence. In an analysis evaluating the effect of baseline polymorphisms on treatment outcome, no statistically significant association was observed between the presence of any HCV NS5B variant at baseline and treatment outcome.

Cross Resistance

HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were fully susceptible to other classes of anti-HCV agents and were 3-10 fold more sensitive to ribavirin as compared to wild-type replicons. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. Sofosbuvir was fully active against substitutions associated with resistance to other DAAs with different mechanisms of actions, such as NS5B non-nucleoside inhibitor, NS3 protease inhibitors and NS5A inhibitors.

Cytotoxicity

Sofosbuvir showed little or no cytotoxicity in cell lines derived from liver, prostate, lymphoid, or connective tissues or primary human cells isolated from the liver, circulating lymphoid cells, or bone marrow.

TOXICOLOGY

Repeat-Dose Toxicity

Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, were evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary target organs identified were the cardiovascular, hepatobiliary, gastrointestinal (GI) and hematopoietic (erythroid) systems. In 7-day toxicity studies with GS-9851, doses of 2000 mg/kg/day in the rat and 1500 mg/kg/day in the dog resulted in (but were not limited to) increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings in dogs; and heart adverse effects in both rats (eg, multifocal cardiac myofiber degeneration) and dogs (eg, increased QT/QTc intervals). At the adverse dose, exposure levels (based on GS-331007 AUC) in the GS-9851 7-day toxicity studies were at least 28-fold higher than human exposure at 400 mg sofosbuvir. In a second 7-day toxicity study conducted with sofosbuvir alone in rats at doses up to 2000 mg/kg/day, no early mortalities or signs of cardiac toxicity were observed. GS-331007 exposure was 29-fold higher than human exposure at 400 mg sofosbuvir, a margin similar to that observed in the previous 7-day rat study with the stereomeric mixture (GS-9851). Findings in the liver and heart were not observed in long-term studies with GS-9851 or sofosbuvir. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), sofosbuvir effects included (but were not limited to) GI-related clinical signs (eg, soft feces and emesis) and a decrease (eg, approximately 10%) in mean red cell indices that were observed mainly in the high-dose group of dogs. One male dog was euthanized moribund with intestinal hemorrhage. The relationship to sofosbuvir was undetermined. In general, exposure levels in the chronic toxicity studies at the no observed adverse effect level were at least 9-fold (based on an AUC of GS-331007) higher than human exposure at 400 mg sofosbuvir.

Genotoxicity and Carcinogenicity

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+/- transgenic mouse study or a 2-year carcinogenicity study in rats. See the Product Monograph for ribavirin.

Sofosbuvir, when administered as the diastereomeric mixture GS-9851, was not genotoxic in a bacterial mutagenicity assay, in an in vitro chromosome aberration test using human peripheral blood lymphocytes and in an in vivo mouse micronucleus assay.

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

Reproductive and Development Toxicity

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 Product Monograph for ribavirin and peginterferon alfa for additional information.

Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. No teratogenic effects were observed in rat and rabbit developmental toxicity studies with sofosbuvir. Sofosbuvir had no adverse effects on behavior, reproduction, or development of the offspring in the rat pre- and post-natal development study. At the highest dose tested, exposure to the predominant circulating metabolite GS-331007 was at least 8-fold the exposure in humans at the recommended clinical dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through lactation day 20 at daily GS-331007 exposures (AUC) of approximately 12-fold higher than human exposures at the recommended clinical dose.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

SOVALDI®
sofosbuvir tablets

Read this carefully before you start taking **Sovaldi**. Read it again every time you get a refill. This leaflet is a summary. It will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment. Ask whether there is any new information about **Sovaldi**.

Serious Warnings and Precautions

Hepatitis B activity (eg, inflamed liver) may increase when taking antiviral drugs like **Sovaldi**, sometimes leading to liver failure and death. (See the "To help avoid side effects…" section, *Hepatitis B Reactivation*)

What is Sovaldi used for?
- **Sovaldi** treats chronic (lasting longer than 6 months) hepatitis C genotype 1, 2, 3 or 4 infection in adults.
- **Sovaldi** is used in combination with ribavirin or pegylated interferon and ribavirin. Read the ribavirin and/or pegylated interferon patient medication information if your doctor says you should also take ribavirin or pegylated interferon and ribavirin.

How does Sovaldi work?
- **Sovaldi** blocks the virus from making more copies of itself in the body.
- **Sovaldi**, used with other medicines, cures chronic hepatitis C in most patients. Cure means hepatitis C virus is cleared from your blood 3 months after finishing the medicine.

What are the ingredients in Sovaldi?
Each tablet has the following medicines: sofosbuvir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide, cellulose, croscarmellose sodium, mannitol, and microcrystalline cellulose.

Each tablet is covered with the following ingredients that are not medicines: polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, and yellow iron oxide.

Sovaldi comes in the following dosage forms:
Sovaldi comes in yellow tablets. Each tablet has 400 mg of sofosbuvir.

Do not use Sovaldi if:
- you are pregnant or may become pregnant (or if your partner is pregnant or may become

pregnant). Ribavirin may cause birth defects or the death of your unborn baby.
- you are allergic to sofosbuvir or any of the other ingredients in this product. (Read also "What are the ingredients in **Sovaldi**?" above.)

To help avoid side effects and make sure you take your medicine properly, talk to your doctor before you take Sovaldi. Talk about any health problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- have HIV.
- have severe kidney disease.
- have any other medical condition.
- are pregnant or plan to become pregnant. It is NOT known if **Sovaldi** can harm your unborn child.
- are breastfeeding or plan to breastfeed. Do NOT breastfeed while taking **Sovaldi**.
- are taking anything listed in the section "The following may interact with **Sovaldi**".

Your doctor may monitor your blood test results during **Sovaldi** treatment if you have some conditions, for example, to check:
- how well your blood can clot if you take warfarin (Coumadin®) or other similar medicines called vitamin K antagonists, to thin the blood.
- blood sugar levels if you have diabetes.
- immunosuppressant drug levels if you receive immunosuppressive therapy.

Hepatitis B Reactivation

Taking antiviral drugs such as **Sovaldi** may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B.
- you know you have a current hepatitis B infection.
- you have had a previous hepatitis B infection.

Your healthcare provider may do blood tests:

- before hepatitis C treatment.
- to see the hepatitis B levels in your blood.
- and may order hepatitis B treatment.

Ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy and Birth Control

Sovaldi must be used with ribavirin or pegylated interferon and ribavirin. Ribavirin may cause birth defects and death of your unborn baby. Extreme care must be taken to avoid becoming pregnant.

- Females must have a negative pregnancy test before starting **Sovaldi** and ribavirin, every month while on the medicine, and for 6 months after stopping them.
- You or your partner should not become pregnant while taking **Sovaldi** with ribavirin and for 6 months after you have stopped taking them.
- You and your partner must use 2 kinds of birth control while taking **Sovaldi** and ribavirin and for 6 months after you have stopped taking them.
- Talk to your doctor about the kind of birth control you can use.
- If you or your partner becomes pregnant while taking **Sovaldi** and ribavirin or within 6 months after you stop taking them, tell your doctor right away.

Another warning you should know about:

Do not take **Sovaldi** with any other medicines containing sofosbuvir (eg, **Harvoni**®, **Epclusa**®, **Vosevi**®).

Tell your doctor about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sovaldi:

- amiodarone (Cordarone®), a drug used to treat irregular heartbeats.
- carbamazepine (Tegretol®), a drug used to treat seizures, nerve pain and bipolar disorder.
- phenobarbital, a drug used to treat anxiety and to control seizures.
- phenytoin (Dilantin®), a drug used to control seizures.
- rifampin (Rifadin®, Rifater®, Rofact®), a drug used to treat tuberculosis.
- rifapentine*, a drug used to treat tuberculosis.
- St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety or depression.

*Not sold in Canada.

How to take Sovaldi:

- Do not take this medicine alone. It must be used with other medicines. You might not need to take pegylated interferon or you might be able to shorten your time on pegylated interferon. Your doctor will tell you what other medicines you should take with **Sovaldi**.
- Take this medicine with or without food.
- Your doctor will tell you how long you need to take this medicine. It can be for 12 or 24 weeks.
- Do NOT stop taking **Sovaldi** without first talking with your doctor.

Usual adult dose:

- Take one tablet once each day.

Overdose:

If you think you have taken too much **Sovaldi**, contact your doctor or pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
It is important to take **Sovaldi** each day.

- **If you miss a dose** of **Sovaldi**, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Sovaldi** and it is almost time for your next dose, wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What to do if you vomit (throw up):

- If you vomit **less than 2 hours** after taking **Sovaldi**, take another tablet.
- If you vomit **more than 2 hours** after taking **Sovaldi**, wait. Do NOT take another tablet until you are scheduled to take the next tablet.

What are possible side effects from using Sovaldi?

If your side effect is not listed here, contact your doctor or pharmacist.

Common side effects when **Sovaldi** is used with ribavirin:

- feeling tired.
- headache.
- trouble sleeping.
- feeling sad or annoyed.
- nausea.
- low red blood cells (in a blood test).

Common side effects when **Sovaldi** is used with ribavirin and pegylated interferon:

- feeling tired.
- headache.
- trouble sleeping.
- feeling sad or annoyed.
- rash.
- nausea.
- low red blood cells or white blood cells (in a blood test).

When **Sovaldi** is used with other hepatitis C medicines (eg, daclatasvir [Daklinza®], simeprevir [Galexos®], or ledipasvir) and amiodarone (a heart drug), side effects may be:

- slow heart beat leading to a need for a pacemaker or death.

Contact your doctor immediately if you have symptoms of a slow heartbeat such as:

- fainting or near-fainting.
- dizziness or lightheadedness.
- not feeling well.
- feeling weak or very tired.
- shortness of breath.
- chest pains.
- confusion or memory problems.

When **Sovaldi** is used with pegylated interferon and ribavirin, the following serious side effects have occurred:

Serious side effects and what to do about them			
Symptom / effect*	Talk to your doctor		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<u>VERY COMMON</u> **Low red blood cells (anemia) with symptoms such as:** • feeling tired • headache • shortness of breath • dizziness • looking pale		✓	
Low white blood cells (neutropenia) with symptoms such as: • increased infections		✓	
Low blood platelets (thrombocytopenia), with symptoms such as: • bruising and increased chance of bleeding		✓	

*These side effects are commonly associated with peginterferon alfa and ribavirin therapy.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your doctor.

Reporting side effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:
- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your doctor if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
- Store **Sovaldi** at 15 to 30°C (59 to 86°F).
- Keep **Sovaldi** in its original container.
- Do NOT use **Sovaldi** if the seal over the bottle opening is broken or missing.
- Keep this medication where children cannot reach it or see it.

If you want more information about Sovaldi:
- Talk to your doctor.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website www.gilead.ca, or by calling 1-800-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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