# Product Monograph

# Pr SOVALDI®

# (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<br>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

### 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 (e.g. 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 direct acting antiviral (DAA) is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered SOVALDI and another DAA:

- Counsel patients about the risk of 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).

**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.

**Patients Coinfected with HBV/HCV:**

The safety and efficacy of SOVALDI have not been established in patients coinfected with HBV.

**Post-Liver Transplant Patients:**

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

## 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%) |

| | 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) |
|---|---|---|---|---|---|
| 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, | Asthenia, chest discomfort, chills, feeling abnormal, injection site rash, injection site reaction, pain, pyrexia, spinal pain |

| Body System | SOVALDI + RBV | SOVALDI + PEG-IFN + RBV |
|---|---|---|
| | pyrexia, xerosis | |
| **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 |
| **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 |

| Body System | SOVALDI + RBV | SOVALDI + PEG-IFN + RBV |
|---|---|---|
| **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 Coinfected Patients*

The safety profile of SOVALDI and ribavirin in HIV-1 coinfected 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 coinfected 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 direct acting antiviral (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 (e.g. rifampin or St. John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of SOVALDI and thus should not be used with SOVALDI (see **WARNINGS AND PRECAUTIONS**). 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:**<br>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:**<br>carbamazepine<br>phenytoin<br>phenobarbital<br>oxcarbazepine | ↓ sofosbuvir<br>↓ GS-331007 | Coadministration of SOVALDI with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended. |
| **Antimycobacterials:**<br>rifabutin<br>rifampin | ↓ sofosbuvir<br>↓ GS-331007 | Coadministration of SOVALDI with rifabutin is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended.<br>SOVALDI should not be used with rifampin, a potent intestinal P-gp inducer (see **WARNINGS AND PRECAUTIONS, General, Use with Potent P-gp Inducers**) |

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease

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

In addition to the drugs included in Table 4, the interaction between SOVALDI and the following drugs were evaluated in clinical trials and no dose adjustment is needed for either drug: cyclosporine, darunavir/ritonavir, emtricitabine, efavirenz, methadone, oral contraceptives, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

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 | $C_{min}$ |
| 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 |
| 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 |
| 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 |

| 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 | $C_{min}$ |
| 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]<br>≥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 (i.e., 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 direct-acting antiviral 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

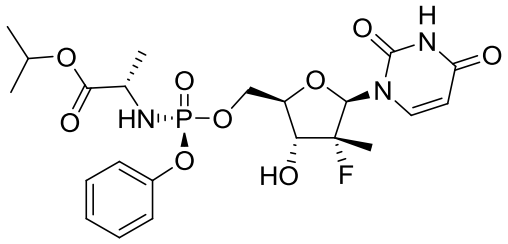
Proper name: sofosbuvir

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 quantification (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<br>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**<br>**Gender: n (%)**<br>Male – 209 (64%)<br>Female – 118 (36%)<br>**Age: median (range)**<br>54 (19–70)<br>**Race: n (%)**<br>White – 257 (79)<br>Black – 54 (17)<br>Asian – 7 (2)<br>Other – 8 (2)<br>Missing – 1<br>**Body Mass Index: mean (range)**<br>29 $kg/m^2$ (18-56 $kg/m^2$)<br>**Baseline HCV RNA Category: n (%)**<br>$\geq 6 \log_{10}$ IU/mL – 256 (78)<br>**Cirrhosis: n (%)**<br>Yes – 54 (17%)<br>**HCV Genotype: n (%)**<br>Genotype 1 – 292 (89)<br>Genotype 4 – 28 (9)<br>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 (e.g., 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)**<br><br>**PEG-IFN 180 µg/week + RBV 800 mg/day; 24 weeks (Comparator Arm)** | **N = 256**<br>**Gender: n (%)**<br>Male 171 (67%)<br>Female 85 (33%)<br>**Age: median (range)**<br>50 (20-72)<br>**Race: n (%)**<br>White – 223 (87)<br>Black – 12 (5)<br>Asian – 14 (6)<br>Other – 7 (3)<br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (17-51 kg/m$^2$)<br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 148 (58)<br>**Cirrhosis: n (%)**<br>Yes – 50 (20%)<br>**HCV Genotype: n (%)**<br>Genotype 1 – 3 (1)<br>Genotype 2 – 70 (27)<br>Genotype 3 – 183 (72) | **N = 243**<br>**Gender: n (%)**<br>Male 156 (64%)<br>Female 87 (36%)<br>**Age: median (range)**<br>50 (19-77)<br>**Race: n (%)**<br>White – 212 (87)<br>Black – 5 (2)<br>Asian – 15 (6)<br>Other – 11 (5)<br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (19-52 kg/m$^2$)<br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 137 (56)<br>**Cirrhosis: n (%)**<br>Yes – 50 (20%)<br>**HCV Genotype: n (%)**<br>Genotype 1 – 0<br>Genotype 2 – 67 (28)<br>Genotype 3 – 176 (72) | **N = 499**<br>**Gender: n (%)**<br>Male 327 (66%)<br>Female 172 (34%)<br>**Age: median (range)**<br>50 (19–77)<br>**Race: n (%)**<br>White – 435 (87)<br>Black – 17 (3)<br>Asian – 29 (6)<br>Other – 18 (4)<br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (17-52 kg/m$^2$)<br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 285 (57)<br>**Cirrhosis: n (%)**<br>Yes – 100 (20%)<br>**HCV Genotype: n (%)**<br>Genotype 1 – 3 (1)<br>Genotype 2 – 137 (27)<br>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 (e.g., 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)**<br><br>**Placebo; 12 weeks (Comparator Arm)** | **N = 207**<br><br>**Gender: n (%)**<br>Male 117 (57%)<br>Female 90 (44%)<br><br>**Age: median (range)**<br>53 (21–75)<br><br>**Race: n (%)**<br>White – 188 (91)<br>Black – 9 (4)<br>Asian – 7 (3)<br>Other – 3 (1)<br><br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (18-53 kg/m$^2$)<br><br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 140 (68)<br><br>**Cirrhosis: n (%)**<br>Yes – 31 (15%)<br><br>**HCV Genotype: n (%)**<br>Genotype 2 – 109 (53)<br>Genotype 3 – 98 (47)<br><br>**Interferon Classification: n (%)**<br>Ineligible – 88 (43)<br>Intolerant – 17 (8)<br>Unwilling – 102 (49)<br><br>**Prior HCV Treatment: n (%)**<br>No – 170 (82) | **N = 71**<br><br>**Gender: n (%)**<br>Male 34 (48%)<br>Female 37 (52%)<br><br>**Age: median (range)**<br>54 (28–67)<br><br>**Race: n (%)**<br>White – 66 (93)<br>Black – 4(6)<br>Asian – 1 (1)<br>Other – 0<br><br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (20-43 kg/m$^2$)<br><br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 54 (76)<br><br>**Cirrhosis: n (%)**<br>Yes – 13 (18%)<br><br>**HCV Genotype: n (%)**<br>Genotype 2 – 34 (48)<br>Genotype 3 – 37 (52)<br><br>**Interferon Classification: n (%)**<br>Ineligible – 33 (47)<br>Intolerant – 8 (11)<br>Unwilling – 30 (42)<br><br>**Prior HCV Treatment: n (%)**<br>No – 56 (79) | **N = 278**<br><br>**Gender: n (%)**<br>Male 151 (54%)<br>Female 127 (46%)<br><br>**Age: median (range)**<br>54 (21-75)<br><br>**Race: n (%)**<br>White – 254 (91)<br>Black – 13 (5)<br>Asian – 8 (3)<br>Other – 3 (1)<br><br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (18-53 kg/m$^2$)<br><br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 194 (70)<br><br>**Cirrhosis: n (%)**<br>Yes – 44 (16%)<br><br>**HCV Genotype: n (%)**<br>Genotype 2 – 143 (51)<br>Genotype 3 – 135 (49)<br><br>**Interferon Classification: n (%)**<br>Ineligible – 121 (44)<br>Intolerant – 25 (9)<br>Unwilling – 132 (47)<br><br>**Prior HCV Treatment: n (%)**<br>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 | Placebo 12 weeks |
|---|---|---|
| | N=207 | N=71 |
| Overall SVR | 78% (161/207) | 0/71 |
| Genotype 2 | 93% (101/109) | 0/34 |
| Genotype 3 | 61% (60/98) | 0/37 |
| <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 (e.g., 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)**<br><br>**SOVALDI 400 mg p.o. + RBV 1000 or 1200 mg p.o. daily; 16 weeks (Treatment Arm 2)** | **N = 103**<br><br>**Gender: n (%)**<br>Male 73 (71%)<br>Female 30 (29%)<br><br>**Age: median (range)**<br>56 (30-69)<br><br>**Race:**<br>White – 88 (85)<br>Black – 5 (5)<br>Asian – 7 (7)<br>Other – 3 (3)<br>Missing – 0<br><br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (19-43 kg/m$^2$)<br><br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 77 (75)<br><br>**Cirrhosis: n (%)**<br>Yes – 36 (35%)<br><br>**HCV Genotype: n (%)**<br>Genotype 1 – 3 (3)<br>Genotype 2 – 36 (35)<br>Genotype 3 – 64 (62)<br><br>**Response to Prior HCV Treatment: n (%)**<br>Relapser – 78 (76) | **N = 98**<br><br>**Gender: n (%)**<br>Male 67 (68%)<br>Female 31 (31%)<br><br>**Age: median (range)**<br>55 (24-70)<br><br>**Race:**<br>White – 86 (88)<br>Black – 1 (1)<br>Asian – 5 (5)<br>Other – 6 (6)<br>Missing – 1 (1)<br><br>**Body Mass Index: mean (range)**<br>29 kg/m$^2$ (20-44 kg/m$^2$)<br><br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 69 (70)<br><br>**Cirrhosis: n (%)**<br>Yes – 32 (33%)<br><br>**HCV Genotype: n (%)**<br>Genotype 1 – 3 (3)<br>Genotype 2 – 32 (33)<br>Genotype 3 – 63 (64)<br><br>**Response to Prior HCV Treatment: n (%)**<br>Relapser – 73 (75) | **N = 201**<br><br>**Gender: n (%)**<br>Male 140 (70%)<br>Female 61 (30%)<br><br>**Age: median (range)**<br>56 (24–70)<br><br>**Race:**<br>White – 174 (87)<br>Black – 6 (3)<br>Asian – 12 (6)<br>Other – 9 (4)<br>Missing – 1 (0.5)<br><br>**Body Mass Index: mean (range)**<br>29 kg/m$^2$ (19-44 kg/m$^2$)<br><br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 146 (73)<br><br>**Cirrhosis: n (%)**<br>Yes – 68 (34%)<br><br>**HCV Genotype: n (%)**<br>Genotype 1 – 6 (3)<br>Genotype 2 – 68 (34)<br>Genotype 3 – 127 (63)<br><br>**Response to Prior HCV Treatment: n (%)**<br>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 (e.g., 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** | **N = 250** | **N = 85** | **N = 419** |
| | **Gender: n (%)**<br>Male - 40 (55)<br>Female - 33 (45) | **Gender: n (%)**<br>Male - 155 (62)<br>Female - 95 (38) | **Gender: n (%)**<br>Male - 49 (58)<br>Female - 36 (42) | **Gender: n (%)**<br>Male - 250 (60)<br>Female - 169 (40) |
| | **Age: median (range)**<br>60 (28–74) | **Age: median (range)**<br>50 (19–69) | **Age: median (range)**<br>51 (19–72) | **Age: median (range)**<br>51 (19–74) |
| | **Race: n (%)**<br>White – 65 (89)<br>Black – 5 (7)<br>Asian – 1 (1)<br>Not permitted – 2 (3) | **Race: n (%)**<br>White – 236 (94)<br>Black – 0<br>Asian – 9 (4)<br>Not permitted – 5 (2) | **Race: n (%)**<br>White – 81 (95)<br>Black – 1 (1)<br>Asian – 3 (4)<br>Not permitted – 0 | **Race: n (%)**<br>White – 393 (94)<br>Black – 6 (1)<br>Asian – 13 (3)<br>Not permitted – 7 (2) |
| | **Body Mass Index: mean (range)**<br>26 kg/m$^2$ (20-35 kg/m$^2$) | **Body Mass Index: mean (range)**<br>25 kg/m$^2$ (17-41 kg/m$^2$) | **Body Mass Index: mean (range)**<br>25 kg/m$^2$ (18-40 kg/m$^2$) | **Body Mass Index: mean (range)**<br>25 kg/m$^2$ (17-44 kg/m$^2$) |
| | **Baseline HCV RNA: median (range)**<br>6.7 $\log_{10}$ IU/mL (4.6-7.6) | **Baseline HCV RNA: median (range)**<br>6.5 $\log_{10}$ IU/mL (3.5-7.6) | **Baseline HCV RNA: median (range)**<br>6.7 $\log_{10}$ IU/mL (4.6-7.4) | **Baseline HCV RNA: median (range)**<br>6.6 $\log_{10}$ IU/mL (3.5-7.6) |
| | **Cirrhosis: n (%)**<br>Yes – 10 (14) | **Cirrhosis: n (%)**<br>Yes – 58 (23) | **Cirrhosis: n (%)**<br>Yes – 18 (21) | **Cirrhosis: n (%)**<br>Yes – 88 (21) |
| | **Prior HCV Treatment Experience And Interferon Classification: n (%)**<br>*Experienced - 41 (56)*<br>IFN Intolerant - 3 (7)<br>Non-Response - 10 (24)<br>Relapse/Breakthrough - 28 (68)<br>*Naïve - 32 (44)*<br>IFN-eligible - 27 (84)<br>IFN-ineligible - 5 (16) | **Prior HCV Treatment Experience And Interferon Classification: n (%)**<br>*Experienced - 145 (58)*<br>IFN Intolerant - 10 (7)<br>Non-Response - 41 (28)<br>Relapse/Breakthrough - 94 (65)<br>*Naïve - 105 (42)*<br>IFN-eligible - 94 (90)<br>IFN-ineligible - 11 (10) | **Prior HCV Treatment Experience And Interferon Classification: n (%)**<br>*Experienced - 50 (59)*<br>IFN Intolerant - 0<br>Non-Response - 18 (36)<br>Relapse/Breakthrough - 32 (64)<br>*Naïve - 35 (41)*<br>IFN-eligible - 30 (86)<br>IFN-ineligible - 5 (14) | **Prior HCV Treatment Experience And Interferon Classification: n (%)**<br>*Experienced - 245 (58)*<br>IFN Intolerant - 13 (5)<br>Non-Response - 73 (30)<br>Relapse/Breakthrough - 159 (65)<br>*Naïve - 174 (42)*<br>IFN-eligible - 153 (88)<br>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 (e.g., 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**

| 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** |
| **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: 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 (e.g., 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 quantification [LLOQ] at 12 weeks post-transplant). HCV-infected subjects, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria (defined as the presence of a tumor 5 cm or less in diameter in patients with single hepatocellular carcinomas and no more than three tumor nodules, each 3 cm or less in diameter in patients with multiple tumors and no extrahepatic manifestations of the cancer or evidence of vascular invasion of tumor) received 400 mg SOVALDI and 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**<br>**Gender: n (%)**<br>Male - 49 (80%)<br>Female - 12 (20%)<br>**Age: median (range)**<br>59 (46–73)<br>**Race:**<br>White – 55 (90)<br>Black – 6 (10)<br>**Body Mass Index: mean (range)**<br>28 kg/m$^2$ (20-59 kg/m$^2$)<br>**Baseline HCV RNA Category: n (%)**<br>≥ 6 $\log_{10}$ IU/mL – 41 (67)<br>**HCV Genotype: n (%)**<br>Genotype 1a – 24 (39)<br>Genotype 1b – 21 (34)<br>Genotype 2a – 1 (2)<br>Genotype 2b – 7 (12)<br>Genotype 3a – 7 (12)<br>Genotype 4a – 1 (2)<br>**IL28B Genotyp: n (%)**<br>CC – 13 (22)<br>non-CC – 48 (78)<br>**Prior HCV Treatment: n (%)**<br>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. $AUC_{0-last}$ 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 (e.g., 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 direct-acting antivirals 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 (e.g. multifocal cardiac myofiber degeneration) and dogs (e.g., 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 (e.g., soft feces and emesis) and a decrease (e.g., 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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**PART III: CONSUMER INFORMATION**

**PrSOVALDI®**
**(sofosbuvir) Tablets**

**This leaflet is part III of a three-part "Product Monograph" published when SOVALDI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SOVALDI. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
SOVALDI is used in combination with ribavirin or pegylated interferon and ribavirin to treat chronic (long term) hepatitis C virus genotype 1, 2, 3, or 4 infection in adults. People with hepatitis C have the virus in their blood and in their liver. It is not known if SOVALDI is safe and effective in children under 18 years of age.

**What it does:**
SOVALDI used with other medicines has been shown to cure chronic hepatitis C infection in the majority of patients. Cure means the HCV virus is cleared from your blood (remains at an undetectable level) when measured 3 months after finishing all treatment.

SOVALDI is a type of medicine called a polymerase inhibitor. It works by blocking a specific step in the replication of the HCV virus. During this specific step, the HCV virus copies its genetic material so that it can create duplicate virus particles. Polymerase inhibitors like SOVALDI prevent the HCV virus from creating a full copy of its genetic material. When SOVALDI is used along with other medicine, many steps in the replication process can be blocked. This prevents the virus particles from duplicating themselves, allowing your body to clear (remove) the virus from your blood.

**When it should not be used:**
Do not take SOVALDI and ribavirin or SOVALDI and ribavirin/peginterferon alfa if you:

- are pregnant or may become pregnant or you are a man whose female partners are pregnant or may become pregnant
- are allergic to sofosbuvir or any of the other ingredients in this product (See "**What the important nonmedicinal ingredients are**")

**What the medicinal ingredient is:**
sofosbuvir

**What the important nonmedicinal ingredients are:**
mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablets are film-coated with a coating material containing polyvinyl alcohol, titanium dioxide, polyethylene glycol/macrogol, talc, and yellow iron oxide.

**What dosage forms it comes in:**
SOVALDI is available as tablets. Each tablet contains sofosbuvir 400 mg, as the active ingredient. 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.

## WARNINGS AND PRECAUTIONS

**BEFORE you use SOVALDI talk to your doctor, nurse, or pharmacist if you:**

- **have liver problems other than hepatitis C infection**
- **have hepatitis B or HIV**
- **have severe kidney disease**
- **have any other medical condition**
- **are pregnant or planning to become pregnant**
- **are breastfeeding. It is not known if SOVALDI passes into your breast milk. You are recommended not to breastfeed while taking SOVALDI.**
- **are taking any medication that is listed in this pamphlet under "Drugs that may interact with SOVALDI" (see INTERACTIONS WITH THIS MEDICATION).**

SOVALDI should not be taken with any other medicine containing sofosbuvir (e.g. HARVONI®).

**Pregnancy**
SOVALDI must be used with ribavirin or peginterferon and ribavirin. Ribavirin may cause birth defects and death of the fetus. Extreme care must be taken to avoid becoming pregnant. This means:

- You or your partner must not become pregnant while taking SOVALDI combination treatment or become pregnant within 6 months after you have stopped taking ribavirin.
- If you or your partner become pregnant during this period, you must contact your doctor.
- Read the package insert for ribavirin for information regarding pregnancy.

**Contraception**
Male and female partners must use 2 effective methods of birth control during the entire treatment and for 6 months after you stop taking SOVALDI combination treatment.

## INTERACTIONS WITH THIS MEDICATION

**Drugs that may interact with SOVALDI include:**

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Other medicines may affect how SOVALDI works.
Especially tell your healthcare provider if you take:

- amiodarone (Cordarone®)
- carbamazepine (Tegretol®)
- oxcarbazepine (Trileptal®)
- phenytoin (Dilantin®)
- phenobarbital
- rifabutin (Mycobutin®)
- rifampin (Rifadin®, Rifater®, Rofact®)
- St. John's wort (*Hypericum perforatum*) or a product that contains St. John's wort

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

## PROPER USE OF THIS MEDICATION

**Usual Adult Dose:**
SOVALDI should not be used alone. Your healthcare provider will tell you what other medicines you should take with SOVALDI.

Take 1 tablet (400 mg) only once daily with or without food.

SOVALDI is taken for either 12 or 24 weeks. Your healthcare provider will tell you exactly how long you need to take SOVALDI.

Do not stop taking SOVALDI without first talking with your healthcare provider.

SOVALDI only works when it is used along with other antiviral medicines. You might not need to take interferon or you might be able to shorten your time on interferon. Your doctor will decide which other medicines you need to use along with SOVALDI.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
It is important not to miss a dose of SOVALDI.

- **If you do miss a dose** of SOVALDI, you must take the tablet as soon as possible. Then take the next dose as usual.
- **If it is nearly 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).

If you are sick (vomit) **less than 2 hours** after taking SOVALDI, take another tablet. If you vomit **more than 2 hours** after taking SOVALDI you should not take another tablet until your next regularly scheduled tablet.

**Do not** take a double dose to make up for a missed dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

- tiredness
- low red blood cells
- headache
- difficulty sleeping
- nausea
- depression
- irritability

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

- tiredness
- low red blood cells
- low white blood cells

- headache
- difficulty sleeping
- nausea
- depression
- rash
- irritability

When SOVALDI is used in conjunction with pegylated interferon and ribavirin, the following effects have occurred:

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| | Symptoms / Effect* | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Very common | **Effect: Low red blood cell counts (anemia)**<br>**Symptoms:**<br>• Tiredness<br>• Headache<br>• Shortness of breath<br>• Dizziness<br>• Looking pale | | ✓ | |
| | **Effect: Low white blood cell counts (neutropenia)**<br>**Symptoms:**<br>• Increased infections | | ✓ | |
| | **Effect: Low blood platelet (thrombocytopenia)**<br>**Symptoms:**<br>• Bruising and increased tendency to bleed | | ✓ | |

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

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of SOVALDI. For more information, ask your healthcare provider or pharmacist.

***This is not a complete list of side effects. For any unexpected effects while taking SOVALDI, contact your doctor or pharmacist.***

## HOW TO STORE IT

Store SOVALDI at 15 – 30 °C (59 – 86 °F).
Keep SOVALDI in its original container.

Do not use SOVALDI if the seal over the bottle opening is broken or missing.
Keep SOVALDI and all medicines out of reach and sight of children.

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
  - **Health Canada**
  - **Postal Locator 0701D**
  - **Ottawa, Ontario**
  - **K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
www.gilead.ca
or by contacting the sponsor, Gilead Sciences Canada, Inc., at:
1–866–207–4267

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