NEW ZEALAND DATA SHEET

1 SOVALDI® (SOFOSBUVIR 400 MG) TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sofosbuvir 400 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

SOVALDI tablets are yellow, capsule shaped debossed with “GSI” on one side and the number “7977” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

SOVALDI is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults and in pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 2 or 3, without cirrhosis or with compensated cirrhosis.

4.2 Dose and method of administraton

4.2.1 Adults

The recommended dose of SOVALDI tablets in adults is 400 mg once daily taken orally with or without food.

SOVALDI should be used in combination with other agents. The recommended dose and treatment duration for SOVALDI combination therapy is provided in Table 1 and Figure 1.

Table 1 Recommended Dose and Treatment Duration for SOVALDI Combination Therapy in Adult Patients

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

* Includes patients co infected with human immunodeficiency virus (HIV).

a. For previously treated patients with HCV genotype 1 infection, no data exists with the combination of SOVALDI, ribavirin and peginterferon alfa
b. Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy).
c. See Special patient populations – Patients awaiting liver transplantation below.

Figure 1 **Illustrative Dosage and Treatment Duration – Interferon-Free Regimens in Adult Patients**

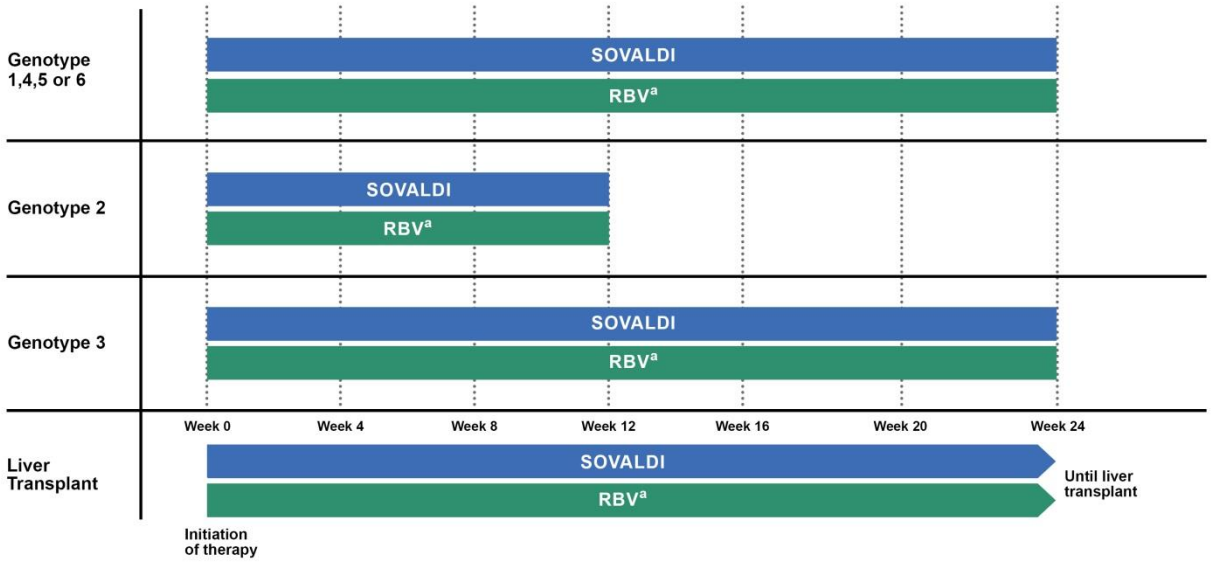
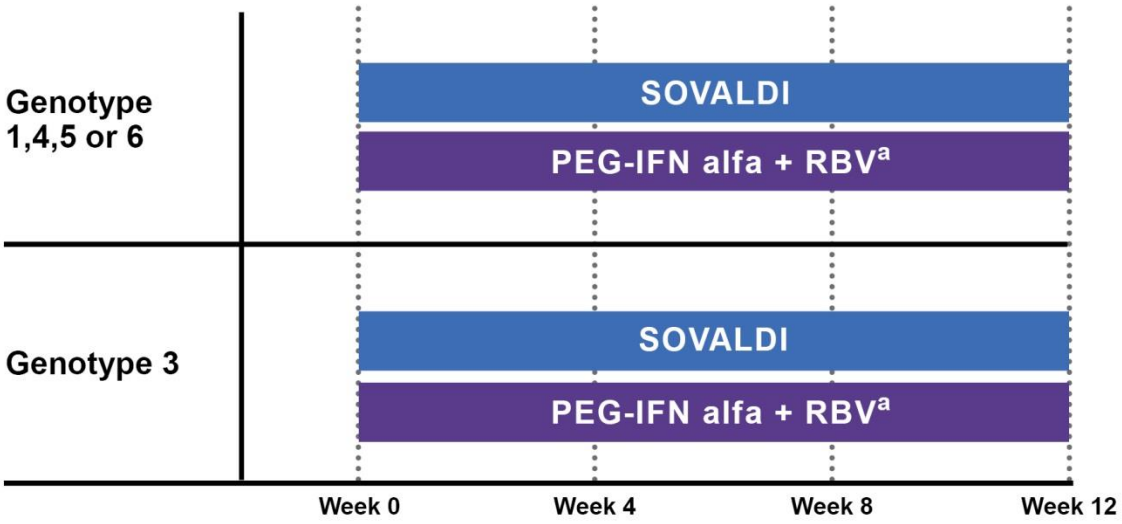


Figure 2 **Illustrative Dosage and Treatment Duration – Interferon-Containing Regimens in Adult Patients**



a. See Ribavirin Dosage requirements (Table 2)

Monotherapy of SOVALDI is not recommended.

Dose Modification

Dose reduction of SOVALDI is not recommended.

Genotype 1, 4, 5 and 6

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

Genotype 2 and 3

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

Table 2 Ribavirin Dose Modification Guideline for Coadministration with SOVALDI in Adults Patients

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day[a] If:	Discontinue Ribavirin If:[b]
Haemoglobin in patients with no cardiac disease	< 10 g/dL	< 8.5 g/dL
Haemoglobin in patients with history of stable cardiac disease	≥ 2 g/dL decrease in haemoglobin during any 4 week period treatment	< 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).

4.2.2 Children and Adolescents up to 18 Years of Age

The recommended dosage of SOVALDI in pediatric patients 12 years of age and older or weighing at least 35 kg is one 400 mg tablet taken orally once daily with or without food in combination with ribavirin (see section 5.1 and section 5.2).

The recommended treatment regimen and duration for SOVALDI combination therapy is provided in Table 3 and Table 4. For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 3. Refer to section 4.5 for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 3 Recommended Dose and Treatment Duration for SOVALDI Combination Therapy in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg

	Patient Population	***Treatment Regimen and Duration***
Genotype 2	Treatment-naïve and treatment experienced[a] without cirrhosis or with compensated cirrhosis (Child-Pugh A)	SOVALDI + ribavirin[b] 12 weeks
Genotype 3	Treatment-naïve and treatment experienced[a] without cirrhosis or with compensated cirrhosis (Child-Pugh A)	SOVALDI + ribavirin[b] 24 weeks

[a] Treatment-experienced patients have failed an interferon based regimen with or without ribavirin.
[b] See Table 4 for weight based ribavirin dosing recommendations.

Table 4 Recommended Dosing for Ribavirin in Combination Therapy with SOVALDI in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg

Body Weight (kg)	**Ribavirin Daily Dose[a]**
< 47	15 mg/kg/day
47-49	600 mg/day
50-65	800 mg/day
66-80	1000 mg/day
>80	1200 mg/day

[a] The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food.

No data are available on which to make a dose recommendation for pediatric patients 12 years of age or under.

Monotherapy of SOVALDI is not recommended.

Discontinuation of Dosing

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

Special populations

Elderly:
Clinical studies of SOVALDI included 62 patients aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment.

Renal impairment:
No dose adjustment of SOVALDI is required for patients with mild or moderate renal impairment. The safety of SOVALDI has not been assessed in patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring haemodialysis (see section 5.2.). 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 section 5.2). Safety and efficacy of SOVALDI have not been established in patients with decompensated cirrhosis. See peginterferon alfa prescribing information for contraindication in hepatic decompensation.

Patients awaiting Liver Transplantation:
SOVALDI in combination with ribavirin was administered for up to 24 weeks to 28 patients with hepatocellular carcinoma awaiting liver transplantation to prevent post-transplant HCV reinfection. The duration of administration of SOVALDI in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient.

4.3 Contraindications

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 prescribing information of peginterferon alfa and ribavirin for a list of their contraindications.

4.4 Special warnings and precautions for use

Pregnancy: Use with Ribavirin

Ribavirin may cause birth defects and/or death of the exposed foetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

When SOVALDI is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential and their male partners must use effective contraception during the treatment and for a period of time after the treatment as recommended in the prescribing information for ribavirin. Refer to ribavirin prescribing information for additional information.

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

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 daclatasvir 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.

Hepatitis B Virus Reactivation

Cases of Hepatitis B virus (HBV) reactivation, including fatal cases, have been reported during and after treatment of HCV with direct-acting antiviral agents (DAAs) in HCV/HBV co-infected patients. Screening for current or past HBV infection, including testing for HBV surface antigen (HBsAg) and HBV core antibody (anti-HBc), should be performed in all patients before initiation of treatment with SOVALDI.

Patients with serologic evidence of current or past HBV infection should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation. Consider initiation of HBV antiviral therapy, if indicated**.**

4.5 Interaction with other medicines and other forms of interaction

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. 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. Coadministration of SOVALDI with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration; accordingly, SOVALDI may be coadministered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of drugs that are substrates of these transporters.

The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity and high capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant drugs.

Drug interaction information for SOVALDI with potential concomitant drugs is summarised in Table 5. The drug interactions described are based on potential drug interactions that may occur with SOVALDI. The table is not all-inclusive.

Table 5 Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Analeptics: modafinil	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended.
Antiarrhythmics: Amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown	Coadministration of amiodarone with SOVALDI in combination with another DAA may result in 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 section 4.4)
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended.
Antimycobacterials: rifabutin rifampin rifapentine	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Such coadministration is not recommended. SOVALDI should not be used with rifampin, a potent intestinal P-gp inducer (see section 4.4)
Herbal Supplements: St. John's wort	↓ sofosbuvir ↓ GS-331007	SOVALDI should not be used with St. John's wort, a potent intestinal P-gp inducer (see section 4.4)

a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease,↔ = no effect

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of sofosbuvir and GS-331007 are shown in Table 6. The effects of sofosbuvir on the exposure of coadministered drugs are shown in Table 7.

Table 6 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}
Cyclosporin	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[c]	600 once daily	400 single dose	16	sofosbuvir	0.81 (0.60, 1.10)	0.94 (0.76, 1.16)	NA
Emtricitabine[c]	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	30 to 130 daily	400 once daily	14	sofosbuvir	0.95[b] (0.68, 1.33)	1.30[b] (1.00, 1.69)	NA
				GS-331007	0.73[b] (0.65, 0.83)	1.04[b] (0.89, 1.22)	NA
Raltegravir	400 once 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
Tacrolimus	5 single dose	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
				GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers

b. Comparison based on historic control

c. Administered as ATRIPLA

Table 7 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}
Cyclosporin	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)
Norelgestromin	Norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily	400 once daily	15	1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel				1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol				1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
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.

Drugs without Clinically Significant Interactions with SOVALDI

In addition to the drugs included in Table 5, the interaction between SOVALDI and the following drugs were evaluated in clinical trials and no dose adjustment is needed for either drug (see above): cyclosporin, darunavir/ritonavir, emtricitabine, efavirenz, methadone, norgestimate/ethinyl estradiol, raltegravir, rilpivirine, tacrolimus (see 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction: Other Forms of Interaction), or tenofovir disoproxil fumarate.

Other Forms of Interaction

Improvement in hepatic function as a result of treatment of HCV with DAAs may require monitoring of relevant laboratory parameters in susceptible patients (e.g., International Normalized Ratio [INR] in patients taking vitamin K antagonists, blood glucose levels in diabetic patients). Concomitant medications significantly affected by changes in hepatic function (e.g., calcineurin inhibitors) may require monitoring or dose modification to ensure continued efficacy.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B2

There are no adequate and well controlled clinical studies with SOVALDI in pregnant women. No effect on foetal development has been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 was approximately 10-fold and 28-fold the exposure in humans at the recommended clinical dose, respectively.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. When SOVALDI is used in combination with ribavirin or peginterferon alfa/ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Women of childbearing potential and their male partners must use effective contraception during treatment and for a period of time after the treatment has concluded as recommended in the prescribing information for ribavirin. Refer to ribavirin prescribing information for additional information.

Breast-feeding

The predominant circulating metabolite GS-331007, but not sofosbuvir, is excreted in rat milk. It is not known whether sofosbuvir and its metabolites are excreted in human breast milk. Mothers should be instructed not to breast-feed if they are taking SOVALDI. See also the prescribing information for ribavirin.

Fertility

Sofosbuvir had no effects on embryo-foetal viability or on fertility when evaluated in rats. At the highest dose tested, exposure to the predominant circulating metabolite GS-331007 was approximately 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.

4.7 Effects on ability to drive and use machines

No studies on the effects of SOVALDI on the ability to drive and use machines have been performed. However, patients should be informed that fatigue and disturbance in attention have been reported during treatment with SOVALDI in combination with ribavirin and fatigue, dizziness, blurred vision and disturbance in attention have been reported during treatment with SOVALDI in combination with peginterferon alfa and ribavirin.

4.8 Undesirable effects

Clinical Trials

4.8.1 Adults

Assessment of adverse reactions is based on pooled Phase 3 data trials (both controlled and uncontrolled) including 650 patients who received SOVALDI + ribavirin combination therapy for 12 weeks, 98 patients who received SOVALDI + ribavirin combination therapy for 16 weeks, 250 patients who received SOVALDI + ribavirin combination therapy for 24 weeks, 327 patients who received SOVALDI + peginterferon alfa + ribavirin combination therapy for 12 weeks, 243 patients who received peginterferon alfa + ribavirin for 24 weeks and 71 patients who received placebo for 12 weeks.

The proportion of patients who permanently discontinued treatment due to adverse events was 4% for patients receiving placebo, 1% for patients receiving SOVALDI + ribavirin for 12 weeks, <1% for patients receiving SOVALDI + ribavirin for 24 weeks, , 11% for patients receiving peginterferon alfa + ribavirin for 24 weeks and 2% for patients receiving SOVALDI + peginterferon alfa + ribavirin for 12 weeks.

No adverse drug reactions specific to SOVALDI have been identified. The following adverse drug reactions have been identified with SOVALDI in combination with ribavirin (Table 8) and with SOVALDI in combination with peginterferon alfa and ribavirin (Table 8).

The adverse reactions are listed below by body system organ class and frequency.

Frequencies are defined as follows: very common ≥ 10%, common ≥ 1% and < 10% or uncommon ≥ 0.1% and < 1%.

Table 8 Adverse Drug Reactions Identified with SOVALDI in Combination with Ribavirin or Peginterferon and ribavirin

Frequency	SOVALDI + ribavirin	SOVALDI + peginterferon alfa + ribavirin
INFECTIONS AND INFESTATIONS		
Common:	Nasopharyngitis	
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Very common:	Haemoglobin decreased	Anaemia, Neutropaenia, Haemoglobin decreased, Lymphocyte count decreased, Neutrophil count decreased, Platelet count decreased, White blood cell count decreased
Common:	Anaemia	
METABOLISM AND NUTRITION DISORDERS		
Very common		Decreased appetite
Common		Weight decreased
PSYCHIATRIC DISORDERS		
Very common:	Insomnia	Insomnia
Common:	Depression	Depression, Anxiety, Agitation
NERVOUS SYSTEM DISORDERS		
Very Common: Common	Disturbance in attention	Dizziness, Headache Migraine, Memory impairment, Disturbance in attention
EYE DISORDERS		
Common		Vision Blurred
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Very Common		Dyspnoea, Cough
Common:	Dyspnoea, Dyspnoea exertional, Cough	Dyspnoea exertional
GASTROINTESTINAL DISORDERS		
Very Common		Diarrhoea, Nausea, Vomiting
Common:	Abdominal discomfort, Constipation, Dyspepsia	Constipation, Dry mouth, Gastroesophageal reflux
HEPATOBILIARY DISORDERS		
Very common:	Blood bilirubin increased	Blood bilirubin increased
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Very Common		Rash, Pruritus
Common:	Alopecia, Dry skin, Pruritus	Alopecia, Dry skin
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Very Common		Arthralgia, Myalgia
Common:	Arthralgia, Back pain, Muscle spasms, Myalgia	Back pain, Muscle spasms
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Very common:	Fatigue, Irritability	Chills, Fatigue, Influenza like illness, Irritability, Pain, Pyrexia
Common:	Pyrexia, Asthenia	Chest pain, Injection site reaction, Asthenia

Other special population(s)

HIV/HCV co-infection
The safety profile of SOVALDI and ribavirin in HCV/HIV co-infected patients was similar to that observed in mono-infected HCV patients treated with SOVALDI and ribavirin in Phase 3 clinical studies.

Patients awaiting liver transplantation
The safety profile of SOVALDI and ribavirin in HCV infected patients prior to liver transplantation was similar to that observed in patients treated with SOVALDI and ribavirin in Phase 3 clinical studies.

Pediatrics
The safety assessment of SOVALDI in pediatric patients 12 years of age and older is based on data from 50 patients who were treated with SOVALDI plus ribavirin for 12 weeks (genotype 2 patients) or 24 weeks (genotype 3 patients) in a Phase 2, open-label clinical trial. The adverse reactions observed were consistent with those observed in clinical studies of SOVALDI plus ribavirin in adults (see section 4.8.1).

Liver transplant recipients
The safety profile of SOVALDI and ribavirin in liver transplant recipients with chronic hepatitis C was similar to that observed in patients treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see CLINICAL TRIALS). In study 0126, decreases in haemoglobin during treatment were very common with 32.5% (13/40 patients) experiencing a decline in haemoglobin to <10 g/dL, 1 of whom also had a decline to <8.5 g/dL. Eight patients (20%) received epoetin and/or a blood product. In 5 patients (12.5%), study drugs were discontinued, modified or interrupted due to adverse events. See Clinical Trials: Liver transplant recipients – Study 0126)

Post Marketing Surveilance
In addition to adverse reactions from clinical studies, the following possible adverse reactions were also identified during postapproval use of SOVALDI. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders
Symptomatic bradycardia (when amiodarone is coadministered with SOVALDI in combination with another HCV direct acting antiviral) [see section 4.4]

Hepatobiliary Disorders
Hepatitis B Reactivation (see section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions:
https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

No specific antidote is available for overdose with SOVALDI. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with SOVALDI consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis can efficiently remove the predominant circulating metabolite GS-331007 with an extraction ratio of 53%.

For information on the management of overdose, contact the National Poisons Centre on 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; direct acting antivirals, other antivirals, ATC code: J05AX15.

Mechanism of action

Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated by HCV NS5B and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with an IC_{50} 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.

Antiviral activity *in vitro*

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 mean ± SD EC_{50} of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.068 ± 0.024 μM for genotype 1a (N=67), 0.11 ± 0.029 μM for genotype 1b (N=29), 0.035 ± 0.018 μM for genotype 2 (N=15) and 0.085 ± 0.034 μM for genotype 3a (N=106). In 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.

Drug 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 including 1b, 1a, 2a, 2b, 3a, 4a, 5a and 6a conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In Clinical Studies:

In a pooled analysis of 991 patients who received SOVALDI in Phase 3 trials, 226 patients 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 patients, with deep sequencing data (assay cutoff of 1%) from 221 of these patients. The NS5B-associated resistance substitution S282T was not detected in any of these patients 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.

Effect of Baseline HCV Polymorphisms on Treatment Outcome

Adults

Baseline NS5B sequences were obtained for 1292 patients 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.

Pediatrics

Baseline NS5B sequences were obtained for 47 patients in the phase 2 study. Among these, one patient was found to have the NS5B resistance associated variant (RAV) substitution F289L and achieved SVR12.

Cross-resistance:

HCV replicons expressing the NS5B-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.

Clinical Data

Adults

The efficacy of SOVALDI was evaluated in five phase 3 trials in a total of 1568 patients with genotypes 1 to 6 chronic hepatitis C (CHC). One study was conducted in treatment-naïve patients with genotype 1, 4, 5 or 6 CHC in combination with peginterferon alfa 2a and ribavirin, and the other four trials were conducted in patients with genotype 2 or 3 CHC in combination with ribavirin including one in treatment-naïve patients, one in interferon intolerant, ineligible or unwilling patients and one in patients previously treated with an interferon-based regimen and one in all patients irrespective of prior treatment history or ability to take interferon. Patients 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. Treatment duration was fixed in each trial and was not guided by patients' 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 (SVR 12).

Clinical Trials in Patients with Genotype 1, 4, 5 or 6 Chronic Hepatitis C

Treatment-Naïve Patients─ NEUTRINO (Study 110)

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

Treated patients (N=327) had a median age of 54 years (range: 19 to 70); 64% of the patients were male; 79% were White, 17% were Black; 14% were Hispanic or Latino; mean body mass index was 29 kg/m^2 (range: 18 to 56 kg/m^2); 78% had baseline HCV RNA greater than 6 $\log_{10}$ IU per mL; 17% had cirrhosis; 89% had HCV genotype 1 and 11% had HCV genotype 4, 5 or 6. 4% were on opiate replacement therapy. Table 9 presents the response rates for the treatment group of SOVALDI + peginterferon alfa + ribavirin.

Table 9 Response Rates in Study NEUTRINO

	SOVALDI + Peg-IFN alfa + RBV 12 weeks
	N=327
Overall SVR	90% (295/327)
Outcome for patients without SVR	
On-treatment virologic failure	0/327
Relapse[a]	9% (28/326)
Other[b]	1% (4/327)

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

Response rates for selected subgroups are presented in Table 10.

Table 10 SVR Rates for Selected Subgroups in NEUTRINO

	SOVALDI + Peg-IFN alfa + RBV 12 weeks
Genotype	
Genotype 1	89% (261/292)
Genotype 4, 5 or 6	97% (34/35)
Cirrhosis	
No	92% (252/273)
Yes	80% (43/54)
Race	
Black	87% (47/54)
Non-black	91% (248/273)

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

Clinical trials in Patients with Genotype 2 or 3 Chronic Hepatitis C

Treatment Naïve Adults ─ FISSION (Study 1231)

FISSION was a randomised, 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 patients 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. Patients were randomised 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). Patients with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio. Treated patients (N=499) had a median age of 50 years (range: 19 to 77); 66% of the patients were male; 87% were White, 3% were Black; 14% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 17 to 52 kg/m^2); 57% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU per mL; 20% had cirrhosis; 72% had HCV genotype 3. 9% were on opiate replacement therapy. Table 11 presents the response rates for the treatment groups of SOVALDI + ribavirin and peginterferon alfa + ribavirin.

Table 11 Response Rates in Study FISSION

	SOVALDI + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	N=256[a]	N=243[a]
Overall SVR	67% (171/253)	67% (162/243)
Genotype 2	95% (60/73)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for patients without SVR		
On-treatment virologic failure	<1% (1/256)	7% (18/243)
Relapse[b]	30% (76/252)	21% (46/217)
Other[c]	3% (8/256)	7% (17/243)

a. The efficacy analysis includes 3 patients with recombinant genotype 2/1 HCV infection.
b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

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) patients achieved SVR in the SOVALDI + ribavirin treatment group compared to 40% (2/5) in the peginterferon alfa + ribavirin treatment group.

Response rates for patients with cirrhosis at baseline are presented in Table 12 by genotype.

Table 12 SVR Rates by Cirrhosis and Genotype in Study FISSION

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

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

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

Treated patients (N=278) had a median age of 54 years (range: 21 to 75); 54% of the patients were male; 91% were White, 5% were Black; 11% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 18 to 53 kg/m^2); 70% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU per mL; 16% had cirrhosis; 49% had HCV genotype 3. 8% were on opiate replacement therapy. The proportions of patients who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most patients had no prior HCV

treatment (81.3%). Table 13 presents the response rates for the treatment groups of SOVALDI + ribavirin and placebo.

Table 13 Response Rates in Study POSITRON

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

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

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

Table 14 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 14 SVR Rates for Selected Subgroups by Genotype in POSITRON

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

Previously Treated Adults ─ FUSION (Study 108)

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

Treated patients (N=201) had a median age of 56 years (range: 24 to 70); 70% of the patients were male; 87% were White; 3% were Black; 9% were Hispanic or Latino; mean body mass index was 29 kg/m^2 (range: 19 to 44 kg/m^2); 73% had baseline HCV RNA levels greater than 6 log_{10} IU per mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. 3% were on opiate replacement therapy. Table 15 presents the response rates for the treatment groups of SOVALDI + ribavirin for 12 weeks and 16 weeks.

Table 15 Response Rates 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)
Outcome for patients without SVR		
On-treatment virologic failure	0/103	0/98
Relapse[b]	48% (49/103)	29% (28/98)
Other[c]	3% (3/103)	0/98

a. The efficacy analysis includes 6 patients with recombinant genotype 2/1 HCV infection.
b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up)

Table 16 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

Table 16 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)

VALENCE was a Phase 3 study that evaluated SOVALDI in combination with weight-based ribavirin for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior interferon-based treatment, including patients with compensated cirrhosis. The study was designed as a direct comparison of SOVALDI and ribavirin *versus* placebo for 12 weeks. However, based on emerging data, the study was unblinded and all HCV genotype 2 patients continued to receive SOVALDI and ribavirin for 12 weeks, whilst treatment for HCV genotype 3 patients was extended to 24 weeks.

Eleven HCV genotype 3 patients had already completed treatment with SOVALDI and ribavirin for 12 weeks at the time of the amendment.

Treated patients (n = 419) had a median age of 51 years (range: 19 to 74); 60% of the patients were male; median body mass index was 25 kg/m^2 (range: 17 to 44 kg/m^2); the mean baseline HCV RNA level was 6.4 $\log_{10}$ IU/mL; 21% had cirrhosis; 78% had HCV genotype 3; 65% were prior relapsers. Table 17 presents the response rates for the treatment groups of SOVALDI+ ribavirin for 12 weeks and 24 weeks.

Placebo recipients are not included in the tables since none achieved SVR12.

Table 17: Response rates in study VALENCE[a]

	Genotype 2 SOVALDI+RBV 12 weeks (n = 73)	**Genotype 3 SOVALDI+RBV 24 weeks (n = 250)**
Overall SVR12	93% (68/73)	84% (210/250)
Outcome for subjects without SVR12		
On-treatment virologic failure	0% (0/73)	<1% (1/250)
Relapse[b]	7% (5/73)	14% (34/249)
Other[c]	0% (0/73)	2% (34/249)

a. Placebo patients(n=85) were not included as none achieved SVR12. Eleven genotype 3 patients who received SOVALDI + ribavirin for 12 weeks were not included

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

c. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 18 presents the subgroup analysis by genotype for cirrhosis and exposure to prior HCV treatment.

Table 18: SVR12 rates for selected subgroups by genotype in study VALENCE

	Genotype 2 SOVALDI+RBV 12 weeks (n = 73)	**Genotype 3 SOVALDI+RBV 24 weeks (n = 250)**
Treatment-naïve	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	94% (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)

SVR12 to SVR24 concordance

The concordance between SVR12 and SVR24 (SVR 24 weeks after the end of the treatment) following treatment with SOVALDI in combination with ribavirin or ribavirin and pegylated interferon demonstrates a positive predictive value of 99% and a negative predictive value of 99%.

Clinical efficacy and safety in special populations

HCV/HIV co-infected patients - PHOTON-1 (study 123)

Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 12 or 24 weeks of treatment with SOVALDI and ribavirin in patients with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were naïve to prior treatment. Patients received 400 mg SOVALDI and weight-based ribavirin (1,000 mg for patients weighing <75 kg or 1,200 mg for patients weighing ≥75 kg) daily for 12 or 24 weeks based on genotype and prior treatment history. Patients 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. Efficacy data 12 weeks post treatment are available for 210 patients (Table 19).

Table 19: Response rates 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 SVR12	76% (87/114)	88% (23/26)	92% (12/13)
Outcome for subjects without SVR12			
On-treatment virologic failure	1% (1/114)	4% (1/26)	0/13
Relapse[b]	22% (25/113)	0/25	8% (1/13)
Other[c]	1% (1/114	8% (2/26)	0/13

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

Table 20 presents the subgroup analysis by genotype for cirrhosis.

Table 20: SVR12 rates for selected subgroups by genotype in study PHOTON-1

	HCV genotype 2		**HCV genotype 3**	
	SOVALDI+RBV 12 weeks TN (n = 26)	**SOVALDI+RBV 24 weeks TE (n = 15)**	**SOVALDI+RBV 12 weeks TN (n = 42)**	**SOVALDI+RBV 24 weeks TE (n = 13)**
Overall	88% (23/26)	93% (14/15)	67% (28/42)	92% (12/13)
No cirrhosis	88% (22/25)	92% (12/13)	67% (24/36)	100% (8/8)
Cirrhosis	100% (1/1)	100% (2/2)	67% (4/6)	80% (4/5)

TN = treatment-naïve; TE = treatment-experienced.

Patients awaiting liver transplantation - Study 2025

SOVALDI was studied in HCV infected patients prior to undergoing liver transplantation in an open-label clinical study evaluating the safety and efficacy of SOVALDI and ribavirin administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the study was post-transplant virologic response (pTVR, HCV RNA <LLOQ at 12 weeks post-transplant). HCV infected patients, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria received 400 mg SOVALDI and 1,000-1,200 mg ribavirin daily for a maximum of 24 weeks, subsequently amended to 48 weeks, or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 patients who received SOVALDI and ribavirin; the majority of patients had HCV genotype 1, 44 patients were CPT class A and 17 patients were CPT class B. Of these 61 patients, 44 patients underwent liver transplantation following up to 48 weeks of treatment with SOVALDI and ribavirin; 41 had HCV RNA <LLOQ at the time of transplantation. The virologic response rates of the 41 patients transplanted with HCV RNA <LLOQ is described in Table 21. 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 21: Virologic response post-transplant in subjects with HCV RNA <LLOQ at the time of liver transplantation

	Week 12 post-transplant (pTVR) [b]
Virologic response in evaluable patients [a]	23/37 (62%)

a. Evaluable patients are defined as those who have reached the specified time point at the time of the interim analysis.
b. pTVR: post-transplant virologic response (HCV RNA <LLOQ at 12 weeks post-procedure).

In patients that discontinued therapy at 24 weeks, according to protocol, the relapse rate was 11/15.

Liver transplant recipients - Study 0126

SOVALDI was studied in an open-label clinical study evaluating the safety and efficacy of 24 weeks of treatment with SOVALDI and ribavirin in liver transplant recipients (N=40) with chronic hepatitis C. Eligible patients were ≥18 years old who had undergone liver or liver/kidney transplantation 6 to 150 months prior to screening and who had HCV RNA $\geq 10^4$ IU/mL at screening and documented evidence of chronic HCV infection pre-transplantation. Key exclusion criteria included: Child-Pugh-Turcotte Score > 7, MELD score > 17, ABO incompatible organ, histological evidence of unresolved rejection, co-infection with hepatitis B or HIV, and history of immunologic disorders. Exclusion criteria also specified use or planned use of T-cell depleting/masking antibodies, systemic antineoplastic agents, cyclosporine > 300 mg/day, sirolimus, everolimus or prednisone ≥ 5mg/day or equivalent.

Forty patients were enrolled and treated, 33 with HCV genotype 1 infection, 6 with HCV genotype 3 infection, and 1 with HCV genotype 4 infection. Thirty-five participants had previously failed interferon-based treatment, and 16 had cirrhosis. SVR was achieved by 28 patients (70% [90% CI 56.0- 81.7%]): 22/33 with HCV genotype 1 infection, 6/6 with HCV genotype 3 infection, and 0/1 with HCV genotype 4 infection. All patients who achieved SVR12 achieved SVR24 and SVR48.

Pediatrics
The efficacy of SOVALDI in HCV-infected patients 12 years of age and older was evaluated in 50 patients with HCV genotype 2 (N = 13) or genotype 3 (N = 37) chronic HCV infection in a Phase 2, open label clinical trial. Patients with HCV genotype 2 or 3 infection in the trial were treated with SOVALDI with ribavirin for 12 or 24 weeks, respectively.

Of the 50 treated patients, the median age was 15 years (range: 12 to 17); 42% of the patients were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 61.1 kg (range: 29.6-100.6 kg); 18% were treatment experienced; 66% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 74% of patients had non-CC IL28B alleles (CT or TT); and no patients had known cirrhosis. The majority of patients (69%) had been infected through vertical transmission.

The SVR12 rate was 100% (13/13) in genotype 2 patients and 97% (36/37) in genotype 3 patients. No patient experienced on-treatment virologic failure or relapse. One patient with genotype 3 HCV infection achieved SVR4 but did not return for the SVR12 visit.

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetic properties of sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult patients and in patients 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.
Based on population pharmacokinetic analysis in patients with genotypes 1 to 6 HCV infection who were coadministered ribavirin (with or withour 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 patients. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1200 mg.

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 patients, the blood to plasma ratio of ^{14}C radioactivity was approximately 0.7.

Metabolism
Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide 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, faeces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-life of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

Effect on food

Relative to fasting conditions, the administration of a single dose of SOVALDI with a standardised 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.

Special Populations

Age, Gender and Ethnicity

No clinically relevant pharmacokinetic differences due to ethnicity have been identified for sofosbuvir and GS-331007.

Sofosbuvir and GS-331007 exposures in pediatric patients 12 years of age and older were similar to those in adults from Phase 2/3 studies following administration of SOVALDI (400 mg). The pharmacokinetics of sofosbuvir and GS-331007 have not been established in pediatric patients less than 12 years of age

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (19 to 75 years) analysed, age did not have a clinically relevant effect on the exposure to sofosbuvir and GS-331007.

No clinically relevant pharmacokinetic differences due to gender or race have been identified for sofosbuvir and GS-331007.

Patients with Impaired Renal Function

The pharmacokinetics of sofosbuvir were studied in HCV negative patients with mild (eGFR $\geq$ 50 and < 80 mL/min/1.73m^2), moderate (eGFR $\geq$ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and patients with end stage renal disease (ESRD) requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In patients with ESRD, relative to patients with normal renal function, sofosbuvir and GS-331007 $AUC_{0\text{-}inf}$ was 28% and 1280% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after haemodialysis. Haemodialysis is required for the elimination of GS-331007 in patients with ESRD, with a 4 hour haemodialysis 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.

Patients with Hepatic Impairment

The pharmacokinetics of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child-Pugh Class B

and C). Relative to patients 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 patients 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.

HCV/HBV Coinfected Patients

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

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:

Mannitol
Microcrystalline cellulose
Croscarmellose sodium
Silicon dioxide
Magnesium stearate

Film-coating:

Polyvinyl alcohol
Titanium dioxide
Macrogol
Talc purified
Iron oxide yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special Precautions for storage

SOVALDI should be stored below 30 °C.

6.5 Nature and contents of container

SOVALDI is supplied in high density polyethylene (HDPE) bottles containing 28 tablets and is closed with a child resistant closure.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements**.**

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Gilead Sciences (NZ)
c/- Grant Thornton New Zealand Limited
L4, 152 Fanshawe Street,
Auckland 1010
New Zealand

Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

21 March 2014

10 DATE OF REVISION OF THE TEXT

13 August 2019

Summary table of changes

Section changed	Summary of new information
4.5	Include language regarding improvement in liver function and monitoring of relevant laboratory parameters in certain patients and the metabolism of other drugs significantly affected by changes in hepatic function.