Product Information

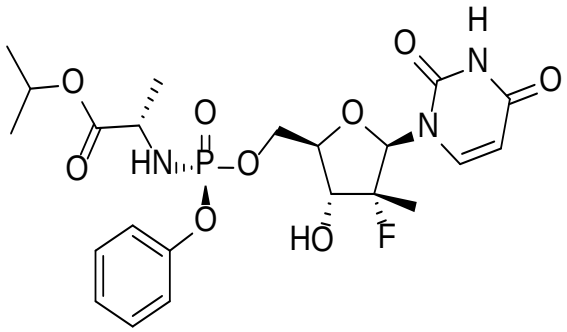
SOVALDI® (sofosbuvir) tablets

NAME OF THE MEDICINE
SOVALDI (400 mg sofosbuvir) tablets.

The active substance in SOVALDI tablets is sofosbuvir.

Sofosbuvir is a nucleotide inhibitor of HCV NS5B RNA-dependent RNA polymerase.

DESCRIPTION
The chemical name of sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula.



CAS registry number: 1190307-88-0

Sofosbuvir is a white to off-white powder with a solubility of ≥ 2 mg/mL across the pH range of 2-7.7 at 37 °C. The partition coefficient (log P) for sofosbuvir is 1.62 and the pKa is 9.3.

SOVALDI tablets contain the following ingredients as <u>excipients:</u>
Tablet core: mannitol, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate.
Film-coating: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc purified, and iron oxide yellow.

Each SOVALDI tablet is film-coated and yellow in colour. The tablets are capsule shaped debossed with "GSI" on one side and the number "7977" on the other side. The tablets are supplied in bottles with child resistant closures.

PHARMACOLOGY

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 *in vitro*.

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 median ± 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

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.

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.

Pharmacokinetics

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 (N=986), steady state AUC_{0-24} for sofosbuvir was 860 ng•hr/ml and steady state AUC_{0-24} and C_{max} for GS-331007 were 7200 ng•hr/mL and 582 ng/mL, respectively. Relative to healthy patients (N=284), the sofosbuvir AUC_{0-24} was 36% higher and the GS-331007 AUC_{0-24} and C_{max} were 39% and 49% 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 of 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.

Age, Gender and Ethnicity
Although not all ethnicities have been studied, no clinically relevant pharmacokinetic differences due to ethnicity have been identified for sofosbuvir and GS-331007.
The pharmacokinetics of sofosbuvir and GS-331007 in paediatric patients has not been established.

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. SOVALDI was administered to 61 subjects aged 65 and over. The response rates observed for subjects over 65 years of age were similar to that of younger subjects across treatment groups (see PRECAUTIONS, Use in Elderly).

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 ≥ 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 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 $AUC_{0\text{-}24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ 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.

CLINICAL TRIALS

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, 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. Ribavirin used in the Phase 3 program was Ribasphere and was deemed to be equivalent to Copegus. 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 LLOQat 12 weeks after the end of treatment (SVR 12).

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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, 2% were Asian; 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 1 presents the response rates for the treatment group of SOVALDI + peginterferon alfa + ribavirin.

Table 1 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 2.

Table 2 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)[a]
Cirrhosis	
No	92% (252/273)
Yes	80% (43/54)
Race	
Black	87% (47/54)
Non-black	91% (248/273)

a. Limited data are available regarding the use of SOVALDI in patients with genotype 4 (n=28), 5 (n=1), or 6 (n=6) CHC

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, 29% were Asian; 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 3 presents the response rates for the treatment groups of SOVALDI + ribavirin and peginterferon alfa + ribavirin.

Table 3 Response Rates in Study FISSION

	SOVALDI + RBV 12 weeks	**Peg-IFN alfa + RBV 24 weeks**
	N=253[a]	N=243[a]
Overall SVR	67% (170/253)	67% (162/243)
Genotype 2	97% (68/70)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for patients without SVR		
On-treatment virologic failure	<1% (1/253)	7% (18/243)
Relapse[b]	30% (74/249)	21% (46/217)
Other[c]	3% (8/253)	7% (17/243)

a. Three patients were excluded from efficacy analysis because they were classified as genotype 1 by NS5B sequencing assay.
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 4 by genotype.

Table 4 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=70)	(N=67)	(N=183)	(N=176)
Cirrhosis				
No	98% (58/59)	81% (44/54)	61% (89/145)	71% (99/139)
Yes	91% (10/11)	62% (8/13)	34% (13/38)	30% (11/37)

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

POSITRON was a randomized, double-blinded, placebo-controlled trial that evaluated 12 weeks of treatment with SOVALDI and ribavirin (N =207) compared to placebo (N =71) in 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, 8% were Asian; 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 5 presents the response rates for the treatment groups of SOVALDI + ribavirin and placebo.

Table 5 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 6 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 6 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, 12% were Asian; 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 7 presents the response rates for the treatment groups of SOVALDI + ribavirin for 12 weeks and 16 weeks.

Table 7 Response Rates in Study FUSION

	SOVALDI+ RBV 12 weeks	**SOVALDI + RBV 16 weeks**
	N= 100[a]	N=95[a]
Overall SVR	50% (50/100)	73% (69/95)
Genotype 2	86% (31/36)	94% (30/32)
Genotype 3	30% (19/64)	62% (39/63)
Outcome for patients without SVR		
On-treatment virologic failure	0/100	0/95
Relapse[b]	47% (47/100)	27% (26/95)
Other[c]	3% (3/100)	0/95

a. Six patients were excluded from efficacy analysis because they were classified as HCV genotype 1 by NS5B sequencing assay.
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 8 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

Table 8 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=36	N=32	N=64	N=63
Cirrhosis				
No	96% (25/26)	100% (23/23)	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	92% (24/26)	96% (23/24)	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 9 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 9: 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[a]	7% (5/73)	14% (34/249)
Other[a]	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 10 presents the subgroup analysis by genotype for cirrhosis and exposure to prior HCV treatment.

Table 10: 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 11).

There is limited data on the safety and efficacy of SOVALDI in HCV/HIV co-infected patients with untreated HIV.

Table 11: 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. Patients with 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 12 presents the subgroup analysis by genotype for cirrhosis.

Table 12: 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

SOVALDI was studied in HCV-infected patients 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 patients, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria received 400 mg SOVALDI and 1000-1200 mg ribavirin daily for a maximum of 24 weeks or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 patients who received SOVALDI and ribavirin; 45 had genotype 1; 44 patients had a baseline CPT score less than 7. 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, one of whom received an HCV-infected liver. The viral response rates of the 41 patients transplanted with HCV RNA<LLOQ are described in Table 13.

Table 13 Virologic Response Post-Transplant in Patients with HCV RNA < LLOQ at the Time of Liver Transplantation

	Week 12 post-transplant (pTVR)[b]
Virologic response in evaluable patients[c]	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).

c. HCV RNA < LLOQ (less than 25 IU per mL)

INDICATIONS

SOVALDI is indicated for the treatment of adults with chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.

(see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION section for detailed information on the studied combinations, dose regimens, and treatment durations for different subgroups of CHC patients).

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

PRECAUTIONS

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.

Treatment-experienced Patients with genotype 1, 4, 5 and 6 HCV Infection
SOVALDI has not been studied in a Phase 3 study in treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection. Thus, the optimal treatment duration in this population has not been established (see DOSAGE and ADMINSTRATION).

Treatment of Patients with genotype 5 and 6 HCV Infection
The clinical data to support the use of SOVALDI in patients with genotype 5 and 6 HCV infection is very limited.

Interferon-free therapy for genotype 1, 4, 5 and 6 HCV Infection
Interferon-free regimens for patients with genotype 1, 4, 5 and 6 HCV infection with SOVALDI have not been fully investigated in Phase 3 studies. The optimal regimen and treatment duration have not been established. Such regimens should only be used for patients that are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment.

HCV/HBV (hepatitis B virus) Coinfected Patients
The safety and efficacy of SOVALDI has not been established in patients coinfected with HBV.

HCV/HIV Coinfected Patients
There is limited data on the safety and efficacy of SOVALDI in HCV/HIV co-infected patients with untreated HIV (see CLINICALTRIALS; HCV/HIV co-infected patients – PHOTON-1 (study 123)).

Post-Liver Transplant Patients
The safety and efficacy of SOVALDI has not been established in post-liver transplant patients.

Long-Term Use of SOVALDI
There is currently no long term safety data on the use of SOVALDI (beyond 24 weeks).

Impairment of Fertility
SOVALDI:
Sofosbuvir had no effects on fertility in male or female rats, at the highest test dose of 500 mg/kg/day, estimated exposure (AUC) to the main metabolite GS-331007 was about 12-fold higher than in humans at the recommended clinical dose.

In a pre- and post-natal developmental study, 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) approximately 12-fold higher than human exposures at the recommended clinical dose**.**

Use with ribavirin or peginterferon:
In fertility studies in animals, ribavirin caused reversible testicular toxicity in males, while perinterferon alfa may impair fertility in females. Refer to the product information for ribavirin and peginterferon for additional information.

Use in Pregnancy: SOVALDI (Pregnancy Category B1)
SOVALDI must not be used as monotherapy (see INDICATIONS). There are no adequate and well controlled clinical studies with SOVALDI in pregnant women. No effect on fetal 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.

Use in Pregnancy: Use with ribavirin or peginterferon (Pregnancy Category X)
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 approximately six months after the treatment has concluded as recommended in the product information for ribavirin. If ribavirin is co-administered with SOVALDI, the contraindications regarding use of ribavirin apply (refer to ribavirin product information).

Use in Lactation
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 product information for ribavirin and peginterferon alfa..

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

Use in the Elderly
SOVALDI was administered to 61 subjects aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups. No dose adjustment of SOVALDI is warranted in elderly patients. In general, caution should be exercised when administering SOVALDI in elderly patients, reflecting the greater frequency of anaemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Genotoxicity
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. See also the product information for ribavirin and peginterferon alfa.

Carcinogenicity

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 200 mg/kg/day in male mice and 600 mg/kg/day in female mice and 750 mg/kg/day in rats. Exposure to GS-331007 in these studies in mice was up to 7 x (male) and 30 x (female) and in rats up to 13 x (male) and 17 x (female) higher than the clinical exposure at 400 mg sofosbuvir. See also the product information for ribavirin and peginterferon alfa.

INTERACTIONS WITH OTHER MEDICINES

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.

The effects of coadministered drugs on the exposure of sofosbuvir and GS-331007 are shown in Table 14. The effects of sofosbuvir on the exposure of coadministered drugs are shown in Table 15.

Table 14 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] Emtricitabine[c]	600 once daily 200 once daily	400 single dose	16	sofosbuvir	0.81 (0.60, 1.10)	0.94 (0.76, 1.16)	NA
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[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 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
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 15 Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence 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)
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
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)

NA = not available/not applicable

a. All interaction studies conducted in healthy volunteers.

b. Administered as ATRIPLA.

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.

Co-administration of ribavirin and didanosine in HIV-HCV co-infected patients is not permitted, please refer to ribavirin product information for guidance.

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 summarized in Table 16. The drug interactions described are based on potential drug interactions that may occur with SOVALDI. The table is not all-inclusive.

Table 16 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.
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 **Precautions: Use with Potent P-gp Inducers**)
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 **Precautions for Use: Use with Potent P-gp Inducers**)
HIV Protease Inhibitors: Tipranavir/ritonavir[c]	↓ sofosbuvir ↓ GS-331007	Coadministration of SOVALDI with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended,

a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease
c. No dosage adjustment is needed when SOVALDI is coadministered with ritonavir and other protease inhibitors

Drugs without Clinically Significant Interactions with SOVALDI

In addition to the drugs included in Table 14, the interaction between SOVALDI and the following drugs were evaluated in clinical trials and no dose adjustment is needed for either drug (see Tables 14 and 15 above): cyclosporin, darunavir/ritonavir, emtricitabine, efavirenz, methadone, raltegravir, rilpivirine, tacrolimus, tenofovir disoproxil fumarate or oral contraceptives (norgestimate/ethinyl estradiol).

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.

ADVERSE EFFECTS

CLINICAL TRIALS

Assessment of adverse reactions is based on pooled Phase 3 data (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 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.

Treatment-emergent adverse events observed in ≥15% of patients in clinical trials are provided in Table 17. A side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

The most common adverse events (≥ 20%) for SOVALDI + ribavirin combination therapy were fatigue and headache. The most common adverse events (≥ 20%) for SOVALDI + peginterferon alfa + ribavirin combination therapy were fatigue, headache, nausea, insomnia and anaemia.

Table 17 Treatment-Emergent Adverse Drug Reactions (Grade 2 and Higher) Reported in at ≥ 15% of Patients in Any Treatment Arm[a,b]

	Interferon-free Regimens			Interferon-containing Regimens	
	PBO 12 weeks	SOVALDI +RBV 12 weeks	SOVALDI +RBV 24 weeks (N=98)	PEG+RBV 24 weeks	SOVALDI +PEG+RBV 12 weeks
	N=71	N=650	N=250	N=243	N=327
Fatigue	24%	38%	30%	55%	59%
Headache	20%	24%	30%	44%	36%
Nausea	18%	22%	13%	29%	34%
Insomnia	4%	15%	16%	29%	25%
Pruritus	8%	11%	27%	17%	17%
Anaemia	0%	10%	6%	12%	21%
Asthenia	3%	6%	21%	3%	5%
Rash	8%	8%	9%	18%	18%
Decreased Appetite	10%	6%	6%	18%	18%
Chills	1%	2%	2%	18%	17%
Influenza Like Illness	3%	3%	6%	18%	16%
Pyrexia	0%	4%	4%	14%	18%
Diarrhoea	6%	9%	12%	17%	12%
Neutropenia	0%	<1%	<1%	12%	17%
Myalgia	0%	6%	9%	16%	14%
Irritability	1%	10%	10%	16%	13%

a Patients received weight-based ribavirin (1000 mg per day if weighing < 75 kg or 1200 mg per day if weighing ≥ 75 kg)
b Patients received 800 mg ribavirin per day regardless of weight.

With the exception of anaemia and neutropenia, the majority of events presented in Table 17 occurred at severity of grade 1 in SOVALDI-containing regimens.

Less Common Adverse Reactions Reported in Clinical Trials (<1%): The following ADRs occurred in <1% of patients receiving SOVALDI in a combination regimen in any one trial. These events have been included because of their seriousness or assessment of potential causal relationship.

Haematologic Effects: pancytopenia (particularly in patients receiving concomitant pegylated interferon).

Psychiatric Disorders: severe depression (particularly in patients with pre-existing history of psychiatric illness), including suicidal ideation and suicide.

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.

DOSAGE AND ADMINISTRATION

The recommended dose of SOVALDI tablets 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 18 and Figure 1.

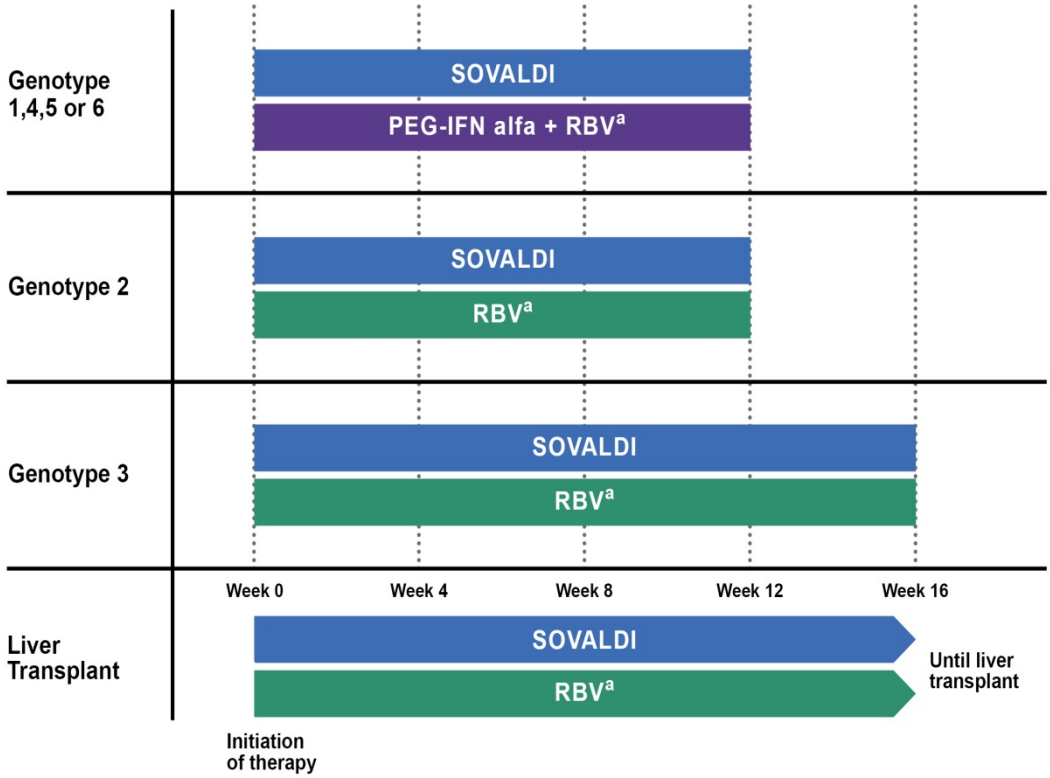
Table 18 Recommended Dose and Treatment Duration for SOVALDI Combination Therapy

	Duration	SOVALDI Dose (daily)	Peginterferon alfa Dose	Ribavirin Dose (daily)
Patients with genotype 1, 4, 5 or 6 CHC	12 weeks [a,b]	400 mg	See peginterferon alfa product information[c]	See ribavirin product information[d]
Patients with genotype 2 CHC	12 weeks		NA	<75 kg = 1000 mg[c] ≥75 kg = 1200 mg[c]
Patients with genotype 3 CHC	16 weeks[e]			
Patients with CHC awaiting liver transplantation	Until liver transplantation[f]			

NA = not applicable

a. For previously treated patients with HCV genotype 1 infection, no data exists with the combination of SOVALDI, ribavirin and peginterferon alfa (see CLINICAL TRIALS)
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. For patients with genotype 5 or 6 CHC, refer to the dosing recommendation for patients with genotype 1 or 4 CHC.
d. The dose of ribavirin, when used in combination with SOVALDI, is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg) and administered orally in two divided doses with food.
e Consideration should be given to potentially extending the duration of therapy beyond 16 weeks and up to 24 weeks guided by an assessment of the potential benefits and risks for the individual patient (these factors may include cirrhosis status and treatment history)
f. See Dosing Recommendations: Special Patient Populations.

Figure 1 Illustrative Dosage and Treatment Duration



a. See Ribavirin Dosage requirements (Table 19). Ribasphere was used in the Phase 3 studies (See CLINICAL TRIALS).

Monotherapy of SOVALDI is not recommended.

Special Patient Populations:

Children and Adolescents up to 18 Years of Age: No data are available on which to make a dose recommendation for children < 18 years of age.

Elderly: No dose adjustment is warranted for elderly patients

Patients with 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 (eGFR < 30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring haemodialysis (see: PHARMACOKINETICS). There are no data to support SOVALDI in patients with severe renal failure. Refer also to ribavirin product information for patients with CrCL < 50 mL/min.

Patients with 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 PHARMACOKINETICS). Safety and efficacy of SOVALDI have not been established in

patients with decompensated cirrhosis. See peginterferon alfa product 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.

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 product 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 19 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 19 Ribavirin Dose Modification Guideline for Coadministration with SOVALDI

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day[a] If:	Discontinue Ribavirin If:[b]
Haemoglobin in patients with no cardiac disease	< 100 g/L	< 85 g/L
Haemoglobin in patients with history of stable cardiac disease	≥ 20 g/L decrease in haemoglobin during any 4 week period treatment	< 120 g/L 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 other agents used in combination with SOVALDI are permanently discontinued, SOVALDI should also be discontinued.

OVERDOSAGE

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 Poison Information Centre on 131126 (Australia) and 0800 764 766 (New Zealand).

PRESENTATION AND STORAGE CONDITIONS

SOVALDI is available as 400 mg tablets, which contain 400 mg sofosbuvir and are yellow, capsule shaped, film coated with "GSI" on one side and "7977" on the other side.

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

SOVALDI should be stored below 30 °C.

NAME AND ADDRESS OF THE SPONSOR

Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne, Victoria 3004

POISON SCHEDULE OF THE DRUG

S4

DATE OF INCLUSION ON ARTG:

30 June 2014