WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sofosbuvir Tablets, Film-coated 400 mg[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains sofosbuvir 400 mg.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Peach coloured, capsule shaped, binconvex, beveled edge film-coated tablets debossed with "SF400" on one side of the tablet and "M" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Sofosbuvir Tablets, Film-coated 400 mg is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to <18 years (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.

4.2 Posology and method of administration

Sofosbuvir Tablets, Film-coated 400 mg treatment should be initiated and monitored by a health care provider experienced in the management of patients with CHC.

Posology

The recommended dose is one 400 mg tablet, taken orally, once daily with food (see section 5.2).

Sofosbuvir Tablets, Film-coated 400 mg should be used in combination with other medicinal products.

Monotherapy of sofosbuvir is not recommended (see section 5.1). The recommended posology of sofosbuvir in combination with ribavirin and peginterferon alfa is provided in Tables 1, 3 and 4.

For information on the direct- acting antivirals against CHC that are used in combination with sofosbuvir, e.g. daclatasvir, refer to the respective summary of product characteristics. This is particularly relevant for the hepatitis C virus (HCV) genotype specificities and dosing recommendations for specific patient populations.

Adults

Table 1: Recommended treatment duration for sofosbuvir combination therapy with ribavirin and ribavirin/peginterferon alfa in adults

[1] Trade names are not prequalified by WHO. This is national medicines regulatory authority's (NMRA) responsiblity. Throughout this WHOPAR the proprietary name is given as an example only.

Patient population*	**Treatment**	**Duration**
Patients with genotype 1, 4, 5 or 6 CHC	sofosbuvir + ribavirin + peginterferon alfa	12 weeks[a,b]
	sofosbuvir + ribavirin Only for use in patients ineligible or intolerant to peginterferon alfa (see section 4.4)	24 weeks
Patients with genotype 2 CHC	sofosbuvir + ribavirin	12 weeks[b]
Patients with genotype 3 CHC	sofosbuvir + ribavirin + peginterferon alfa	12 weeks[b]
	sofosbuvir + ribavirin	24 weeks
Patients with CHC awaiting liver transplantation	sofosbuvir + 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 sofosbuvir, ribavirin and peginterferon alfa (see section 4.4).

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.

The dose of ribavirin, when used in combination with sofosbuvir is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg) and administered orally in two divided doses with food.

Concerning co-administration with other direct-acting antivirals against HCV, see section 4.4 and the summary of product characteristics of the respective products.

Dose modification
Dose reduction of sofosbuvir is not recommended.

If sofosbuvir is used in combination with peginterferon alfa, and a patient has a serious adverse reaction potentially related to this drug, the peginterferon alfa dose should be reduced or discontinued. Refer to the peginterferon alfa summary of product characteristics for additional information about how to reduce and/or discontinue the peginterferon alfa dose.

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 co-administration with sofosbuvir

Laboratory values	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Haemoglobin in subjects with no cardiac disease	<10 g/dL	<8.5 g/dL
Haemoglobin in subjects with history of stable cardiac disease	≥2 g/dL decrease in haemoglobin during any 4 week treatment period	<12 g/dL despite 4 weeks at reduced dose

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 (1,000 mg to 1,200 mg daily).

Paediatric population

Table 3: Recommended treatment duration for sofosbuvir combination therapy with ribavirin and ribavirin/peginterferon alfa in adolescents

Patient population*	Treatment and duration
Patients with genotype 2 CHC	sofosbuvir + ribavirin[a] for 12 weeks [b]
Patients with genotype 3 CHC	sofosbuvir + ribavirin [a] for 24 weeks

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

a. See Table 4 for weight based ribavirin dosing recommendations

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).

Table 4: Recommended dosing for ribavirin in combination therapy with sofosbuvir in adolescents aged 12 to < 18 years

Body weight kg (lbs)	RBV daily dose*
<47 (<103)	15 mg/kg/day
47-49 (103-108)	600 mg/day
50-65 (110-143)	800 mg/day
66-80 (145-176)	1000 mg/day
>81 (178)	1200 mg/day

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

Dose modification in the paediatric population

Dose reduction of sofosbuvir is not recommended.

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. Refer to the ribavirin prescribing information for guidance on dose modification or discontinuation.

Discontinuation of dosing
If the other medicinal products used in combination with sofosbuvir are permanently discontinued, sofosbuvir should also be discontinued (see section 4.4).

Special patient populations
Elderly
No dose adjustment is warranted for elderly patients (see section 5.2).

Renal impairment
No dose adjustment of sofosbuvir is required for patients with mild or moderate renal impairment. The safety and appropriate dose of sofosbuvir have not been established in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

Hepatic impairment
No dose adjustment of sofosbuvir is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C) (see section 5.2). The safety and efficacy of sofosbuvir have not been established in patients with decompensated cirrhosis.

Patients awaiting liver transplantation
The duration of administration of sofosbuvir in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient (see section 5.1).

Liver transplant recipients
Sofosbuvir in combination with ribavirin is recommended for 24 weeks in liver transplant recipients.
A starting ribavirin dose of 400 mg administered orally in two divided doses with food is recommended. If the starting dose of ribavirin is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (1,000 mg for patients weighing <75 kg and 1,200 mg for patients weighing ≥75 kg). If the starting dose of ribavirin is not well-tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels (see section 5.1).

Paediatric population
The safety and efficacy of sofosbuvir in children and adolescents aged <12 years have not yet been established. No data on paediatric patients < 12 years are available.

Method of administration
The film-coated tablet is for oral use. Patients should be instructed to swallow the tablet whole.
The film-coated tablet should not be chewed or crushed, due to the bitter taste of the active substance. The tablet should be taken with food (see section 5.2).

Patients should be instructed that if vomiting occurs within 2 hours of dosing an additional tablet should be taken. If vomiting occurs more than 2 hours after dosing, no further dose is needed. These recommendations are based on the absorption kinetics of sofosbuvir and its predominant inactive metabolite GS-331007 suggesting that the majority of the dose is absorbed within 2 hours after dosing.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the

usual time.
Patients should be instructed not to take a double dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use with potent P-gp inducers

Medicinal products that are potent P-glycoprotein (P-gp) inducers in the intestine (rifampicin, rifabutin, St. John's wort [Hypericum perforatum], carbamazepine, phenobarbital and phenytoin).
Co-administration will significantly decrease sofosbuvir plasma concentration and could result in loss of efficacy of Sofosbuvir Tablets, Film-coated 400 mg (see section 4.5).

4.4 Special warnings and precautions for use

General
Sofosbuvir Tablets, Film-coated 400 mgis not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection. If the other medicinal products used in combination with sofosbuvir are permanently discontinued, Sofosbuvir Tablets, Film-coated 400 mg should also be discontinued (see section 4.2).
Consult the summary of product characteristics for co-prescribed medicinal products before starting therapy with Sofosbuvir Tablets, Film-coated 400 mg.

Severe bradycardia and heart block
Cases of severe bradycardia and heart block have been observed when sofosbuvir is used in combination with another direct-acting antiviral (DAAs, including daclatasvir and ledipasvir) and concomitant amiodarone with or without other drugs that lower heart rate. The mechanism is not established.

The concomitant use of amiodarone was limited through the clinical development of sofosbuvir plus DAAs. These events are potentially life threatening, therefore amiodarone should only be used in patients on sofosbuvir and another DAA when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated. 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.

Should concomitant use of amiodarone be considered necessary it is recommended that patients are closely monitored when initiating sofosbuvir and another DAA. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir in combination with another DAA.

All patients receiving sofosbuvir and another DAA in combination with amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection
Sofosbuvir has not been studied in a Phase 3 study in treatment-experienced patients with genotype 1, 4, 5 or 6 HCV infection. Thus, the optimal treatment duration in this population has not been established (see also sections 4.2 and 5.1).

Consideration should be given to treating these patients, and potentially extending the duration of therapy with sofosbuvir, peginterferon alfa and ribavirin 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 (advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).

Treatment of patients with genotype 5 or 6 HCV infection
The clinical data to support the use of sofosbuvir in patients with genotype 5 and 6 HCV infection is very limited (see section 5.1).

Interferon-free therapy for genotype 1, 4, 5 and 6 HCV infection
Interferon-free regimens for patients with genotype 1, 4, 5 or 6 HCV infection with sofosbuvir have not been investigated in Phase 3 studies (see section 5.1). 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.

Co-administration with other direct-acting antivirals against HCV
There are no data to support the co-administration of sofosbuvir and boceprevir. Such co-administration is not recommended (see also section 4.5).

Pregnancy and concomitant use with ribavirin
When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential or their male partners must use an effective form of contraception during the treatment and for a period of time after the treatment as recommended in the summary of product characteristics for ribavirin. Refer to the summary of product characteristics for ribavirin for additional information.

Use with moderate P-gp inducers
Medicinal products that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine and modafinil) may decrease sofosbuvir plasma concentration leading to a reduced therapeutic effect. Co-administration of such medicinal products is not recommended with Sofosbuvir Tablets, Film-coated 400 mg (see section 4.5).

Renal impairment
The safety of sofosbuvir has not been assessed in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or ESRD requiring haemodialysis. Furthermore, the appropriate dose has not been established. When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, refer also to the summary of product characteristics for ribavirin for patients with creatinine clearance (CrCl) <50 mL/min (see also section 5.2).

HCV/HBV (hepatitis B virus) co-infection
Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Paediatric population
Sofosbuvir is not recommended for use in children and adolescents under 12 years of age because the safety and efficacy have not been established in this population.

4.5 Interactions with other medicinal products and other forms of interaction

Sofosbuvir is a nucleotide prodrug. After oral administration sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic and intestinal metabolism. Intracellular hydrolytic prodrug cleavage catalysed by enzymes including carboxylesterase 1 and sequential phosphorylation steps catalysed by nucleotide kinases result in formation of the pharmacologically active uridine nucleoside analogue triphosphate. The predominant inactive circulating metabolite GS-331007 that accounts for greater than 90% of drug-related material systemic exposure is formed through pathways sequential and parallel to formation of active metabolite. The parent sofosbuvir accounts for approximately 4% of drug-related material systemic exposure (see section 5.2). 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.

Medicinal products that are potent P-gp inducers in the intestine (rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may significantly decrease sofosbuvir plasma concentration leading to a reduced therapeutic effect of {DotWP-ProductName} and thus are contraindicated with sofosbuvir (see section 4.3). Medicinal products that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine and modafinil) may decrease sofosbuvir plasma concentrations leading to reduced therapeutic effect of {DotWP-ProductName}. Co-administration of sofosbuvir with such medicinal products is not recommended (see section 4.4). Co-administration of sofosbuvir with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus sofosbuvir may be co-administered 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 medicinal products 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 medicinal products (see section 5.2).

Patients treated with vitamin K antagonists

As liver function may change during treatment with sofosbuvir, the International Normalised Ratio (INR) values should be closely monitored.

Other interactions

Drug interaction information for sofosbuvir with potential concomitant medicinal products is summarised in Table 3 below (where 90% confidence interval (CI) of the geometric least-squares mean (GLSM) ratio were within "↔", extended above "↑", or extended below "↓" the predetermined equivalence boundaries). The table is not all-inclusive.

Table 3: Interactions between sofosbuvir and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendation concerning co-administration with Sofosbuvir Tablets, Film-coated 400 mg**
ANALEPTICS		
Modafinil	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007	Co-administration of sofosbuvir with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.
ANTIARRHYTHMICS		

Amiodarone	Interaction not studied.	Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with sofosbuvir and another DAA (see sections 4.4 and 4.8).
ANTICOAGULANTS		
Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendation concerning co-administration with Sofosbuvir Tablets, Film coated 400 mg**
Vitamin K antagonists	Interaction not studied	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with sofosbuvir.
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir is contraindicated with carbamazepine, phenobarbital and phenytoin, potent intestinal P-gp inducers (see section 4.3).
Oxcarbazepine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007	Co-administration of sofosbuvir with oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to a reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended (see section 4.4).
ANTIMYCOBACTERIALS		
Rifampicin[1] (600 mg SD)	*Sofosbuvir* ↓↓ C_{max} ↓↓ AUC C_{min} (NA) *GS-331007* ↔ C_{max} ↔ AUC C_{min} (NA)	Sofosbuvir is contraindicated with rifampicin, a potent intestinal P-gp inducer (see section 4.3).
Rifabutin Rifapentine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir is contraindicated with rifabutin, a potent intestinal P-gp inducer (see section 4.3). Co-administration of sofosbuvir with rifapentine is expected to decrease the concentration of sofosbuvir, leading to a reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.
Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendation concerning co-administration with Sofosbuvir Tablets, Film-coated 400 mg**

HERBAL SUPPLEMENTS		
St. John's wort *(Hypericum perforatum)*	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007	Sofosbuvir is contraindicated with St. John's wort, a potent intestinal P-gp inducer (see section 4.3).
HBV ANTIVIRAL AGENTS		
Entecavir	Interaction not studied. Based on the metabolism and clearance a clinically significant drug-drug interaction is unlikely.	No dose adjustment of sofosbuvir or entecavir is required when these agents are used concomitantly.
HCV DIRECT-ACTING ANTIVIRALS		
Boceprevir (BOC)	Interaction not studied. *Expected:* ↔ Sofosbuvir (BOC) ↔ GS-331007 (BOC)	No drug-drug interaction data exists regarding the co-administration of sofosbuvir with boceprevir.
Daclatasvir (400mg OD)	↔ Daclatasvir GS-331007: ↔ AUC ↓ C_{max} ↑ C_{min}	No dose adjustment of daclatasvir or sofosbuvir is required.
Elbasvir/grazoprevir (50mg + 200mg)	Sofosbuvir ↑ AUC ↑ C_{max} GS-331007 ↔ AUC ↔ C_{max} ↑ C_{trough} Elbasvir/grazoprevir	No dose adjustments of elbasvir/grazoprevir or sofosbuvir are needed.
Glecaprevir/pibrentasvir	Sofosbuvir ↑ AUC ↑ C_{max} GS-331007 ↔ AUC ↔ C_{max} ↑ C_{trough} Glecaprevir/pibrentasvir ↔ AUC ↔ C_{max}	No dose adjustments of glecaprevir/pibrentasvir or sofosbuvir are needed.
Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendation concerning co-administration with Sofosbuvir Tablets, Film-coated 400 mg**
NARCOTIC ANALGESICS		

Methadone[f] (Methadone maintenance therapy [30 to 130 mg/daily])	*R-methadone* ↔ C_{max} 0.99 (0.85, 1.16) ↔ AUC 1.01 (0.85, 1.21) ↔ C_{min} 0.94 (0.77, 1.14) *S-methadone* ↔ C_{max} 0.95 (0.79, 1.13) ↔ AUC 0.95 (0.77, 1.17) ↔ C_{min} 0.95 (0.74, 1.22) *Sofosbuvir* ↓ C_{max} 0.95[c] (0.68, 1.33) ↑ AUC 1.30[c] (1.00, 1.69) C_{min} (NA) *GS-331007* ↓ C_{max} 0.73[c] (0.65, 0.83) ↔ AUC 1.04[c] (0.89, 1.22) C_{min} (NA)	No dose adjustment of sofosbuvir or methadone is required when sofosbuvir and methadone are used concomitantly.
IMMUNOSUPPRESSANTS		
Ciclosporin[e] (600 mg single dose)	*Ciclosporin* ↔ C_{max} 1.06 (0.94, 1.18) ↔ AUC 0.98 (0.85, 1.14) C_{min} (NA) *Sofosbuvir* ↑ C_{max} 2.54 (1.87, 3.45) ↑ AUC 4.53 (3.26, 6.30) C_{min} (NA) *GS-331007* ↓ C_{max} 0.60 (0.53, 0.69) ↔ AUC 1.04 (0.90, 1.20) C_{min} (NA)	No dose adjustment of sofosbuvir or ciclosporin is required when sofosbuvir and ciclosporin are used concomitantly.
Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendation concerning co-administration with Sofosbuvir Tablets, Film-coated 400 mg**

Tacrolimus[e] (5 mg single dose)	*Tacrolimus* ↓ C_{max} 0.73 (0.59, 0.90) ↔ AUC 1.09 (0.84, 1.40) C_{min} (NA) *Sofosbuvir* ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) C_{min} (NA) *GS-331007* ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13) C_{min} (NA)	No dose adjustment of sofosbuvir or tacrolimus is required when sofosbuvir and tacrolimus are used concomitantly.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz[f] (600 mg once daily)[d]	*Efavirenz* ↔ C_{max} 0.95 (0.85, 1.06) ↔ AUC 0.96 (0.91, 1.03) ↔ C_{min} 0.96 (0.93, 0.98) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or efavirenz is required when sofosbuvir and efavirenz are used concomitantly.

Emtricitabine[1] (200 mg once daily)[d]	*Emtricitabine* ↔ C_{max} 0.97 (0.88, 1.07) ↔ AUC 0.99 (0.94, 1.05) ↔ C_{min} 1.04 (0.98, 1.11) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or emtricitabine is required when sofosbuvir and emtricitabine are used concomitantly.
Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendation concerning co-administration with Sofosbuvir Tablets, Film-coated 400 mg**
Tenofovir disoproxil[f] (245 mg once daily)[d]	*Tenofovir* ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07) *Sofosbuvir* ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) *GS-331007* ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or tenofovir disoproxil is required when sofosbuvir and tenofovir disoproxil are used concomitantly.

Rilpivirine[1] (25 mg once daily)	*Rilpivirine* ↔ C_{max} 1.05 (0.97, 1.15) ↔ AUC 1.06 (1.02, 1.09) ↔ C_{min} 0.99 (0.94, 1.04) *Sofosbuvir* ↑ C_{max} 1.21 (0.90, 1.62) ↔ AUC 1.09 (0.94, 1.27) C_{min} (NA) *GS-331007* ↔ C_{max} 1.06 (0.99, 1.14) ↔ AUC 1.01 (0.97, 1.04) C_{min} (NA)	No dose adjustment of sofosbuvir or rilpivirine is required when sofosbuvir and rilpivirine are used concomitantly.
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Darunavir boosted with ritonavir[f] (800/100 mg once daily)	*Darunavir* ↔ C_{max} 0.97 (0.94, 1.01) ↔ AUC 0.97 (0.94, 1.00) ↔ C_{min} 0.86 (0.78, 0.96) *Sofosbuvir* ↑ C_{max} 1.45 (1.10, 1.92) ↑ AUC 1.34 (1.12, 1.59) C_{min} (NA) *GS-331007* ↔ C_{max} 0.97 (0.90, 1.05) ↔ AUC 1.24 (1.18, 1.30) C_{min} (NA)	No dose adjustment of sofosbuvir or darunavir (ritonavir boosted) is required when sofosbuvir and darunavir are used concomitantly. Coadministration with darunavir boosted with cobicistat has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Sofosbuvir is a prodrug and formation of its active metabolite is unlikely to be affected by cobicistat.

Medicinal product by therapeutic areas	**Effects on drug levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a,b]**	**Recommendation concerning co-administration with Sofosbuvir Tablets, Film-coated 400 mg**
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		
Raltegravir[1] (400 mg twice daily)	*Raltegravir* ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{min} 0.95 (0.81, 1.12) *Sofosbuvir* ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) C_{min} (NA) *GS-331007* ↔ C_{max} 1.09 (0.99, 1.20) ↔ AUC 1.03 (0.97, 1.08)	No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly.
ORAL CONTRACEPTIVES		
Norgestimate/ethinyl estradiol	*Norgestromin* ↔ C_{max} 1.06 (0.93, 1.22) ↔ AUC 1.05 (0.92, 1.20) C_{min} (NA) *Norgestrel* ↔ C_{max} 1.18 (0.99, 1.41) ↔ AUC 1.19 (0.98, 1.44) C_{min} (NA) *Ethinyl estradiol* ↔ C_{max} 1.14 (0.96, 1.36) ↔ AUC 1.08 (0.93, 1.25) C_{min} (NA)	No dose adjustment of norgestimate/ethinyl estradiol is required when sofosbuvir and norgestimate/ethinyl estradiol are used concomitantly.

NA = not available/not applicable

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics with/without sofosbuvir and mean ratio of sofosbuvir and GS-331007 with/without co-administered drug. No effect = 1.00

b. All interaction studies conducted in healthy volunteers c. Comparison based on historical control

d. Administered as fixed dose combination of tenofovir disoproxil, emtricitabine and efavirenz

e. Bioequivalence boundary 80%-125%

f. Equivalence boundary 70%-143%

4.6 Pregnancy, breast-feeding and fertility

Women of childbearing potential / contraception in males and females
When sofosbuvir 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. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin (see section 4.4). Women of childbearing potential or their male partners must use an effective form of contraception during treatment and for a period of time after the treatment has concluded. Refer to the summary of product characteristics for ribavirin for additional information.

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of sofosbuvir in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. No effects on foetal development have been observed in rats and rabbits at the highest doses tested. However, it has not been possible to fully estimate exposure margins achieved for sofosbuvir in the rat relative to the exposure in humans at the recommended clinical dose (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of sofosbuvir during pregnancy.

However, if ribavirin is co-administered with sofosbuvir, the contraindications regarding use of ribavirin during pregnancy apply (see also the summary of product characteristics for ribavirin).

Breast-feeding
It is unknown whether sofosbuvir and its metabolites are excreted in human milk.

Available pharmacokinetic data in animals has shown excretion of metabolites in milk (for details see section 5.3).

A risk to newborns/infants cannot be excluded. Therefore, sofosbuvir should not be used during breast-feeding.

Fertility
No human data on the effect of sofosbuvir on fertility are available. Animal studies do not indicate harmful effects on fertility.

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue and disturbance in attention, dizziness and blurred vision have been reported during treatment with sofosbuvir in combination with peginterferon alfa and ribavirin (see section 4.8). This may influence their ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
During treatment with sofosbuvir in combination with ribavirin or with peginterferon alfa and ribavirin, the most frequently reported adverse drug reactions were consistent with the expected safety profile of ribavirin and peginterferon alfa treatment, without increasing the frequency or severity of the expected adverse drug reactions.

Assessment of adverse reactions is based on pooled data from five Phase 3 clinical studies (both controlled and uncontrolled).

The proportion of subjects who permanently discontinued treatment due to adverse reactions was 1.4% for subjects receiving placebo, 0.5% for subjects receiving sofosbuvir + ribavirin for 12 weeks, 0% for subjects receiving sofosbuvir + ribavirin for 16 weeks, 11.1% for subjects receiving peginterferon alfa+ ribavirin for 24 weeks and 2.4% for subjects receiving sofosbuvir + peginterferon alfa + ribavirin for 12 weeks.

Tabulated summary of adverse reactions

Sofosbuvir has mainly been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse drug reactions occurring in subjects receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

The following adverse drug reactions have been identified with sofosbuvir in combination with ribavirin or in combination with peginterferon alfa and ribavirin (Table 4). The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000).

Table 4: Adverse drug reactions identified with sofosbuvir in combination with ribavirin or peginterferon alfa and ribavirin

Frequency	SOF[a] + RBV[b]	SOF + PEG[c] + RBV
Infections and infestations:		
Common	nasopharyngitis	
Blood and lymphatic system disorders:		
Very common	haemoglobin decreased	anaemia, neutropenia, lymphocyte count decreased, platelet 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	headache	dizziness, headache
Common	disturbance in attention	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	nausea	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, asthenia

a. SOF = sofosbuvir; b. RBV = ribavirin; c. PEG = peginterferon alfa.

Other special population(s)

HIV/HCV co-infection

The safety profile of sofosbuvir and ribavirin in HCV/HIV co-infected subjects was similar to that observed in mono-infected HCV subjects treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1).

Patients awaiting liver transplantation

The safety profile of sofosbuvir and ribavirin in HCV infected subjects prior to liver transplantation was similar to that observed in subjects treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1).

Liver transplant recipients

The safety profile of sofosbuvir and ribavirin in liver transplant recipients with chronic hepatitis C was similar to that observed in subjects treated with sofosbuvir and ribavirin in Phase 3 clinical studies (see section 5.1). In study 0126, decreases in haemoglobin during treatment were very common with 32.5% (13/40 subjects) experiencing a decline in haemoglobin to <10 g/dL, 1 of whom also had a decline to <8.5 g/dL. Eight subjects (20%) received epoetin and/or a blood product. In 5 subjects (12.5%), study drugs were discontinued, modified or interrupted due to adverse events.

Paediatric population

The safety and efficacy of sofosbuvir in adolescents aged 12 to <18 years are based on data from 50 patients who were treated with sofosbuvir and ribavirin for 12 weeks (genotype 2 patients) and 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 sofosbuvir plus ribavirin in adults (see Table 6).

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir is used in combination with another DAA (including daclatasvir and ledipasvir) and concomitant amiodarone and/or other drugs that lower heart rate (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1,200 mg administered to 59 healthy subjects. In that study, there were no untoward effects observed at this dose level, and adverse reactions were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups. The effects of higher doses are unknown.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral; 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 into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with a 50% inhibitory concentration (IC_{50}) value ranging from 0.7 to 2.6 μM. GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Resistance
In cell culture
Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, 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 221 samples with post-baseline NS5B sequences and deep sequencing data (assay cutoff of 1%) the sofosbuvir-associated resistance substitution S282T was not detected by deep sequencing or population sequencing. The S282T substitution in NS5B was detected in a single subject receiving sofosbuvir monotherapy in a Phase 2 study. This subject harboured <1% HCV S282T at baseline and developed S282T (>99%) at 4 weeks post-treatment which resulted in a 13.5-fold change in sofosbuvir EC_{50} and reduced viral replication capacity. The S282T substitution reverted to wild-type over the next 8 weeks and was no longer detectable by deep sequencing at 12 weeks post-treatment.

Two NS5B substitutions, L159F and V321A, were detected in post-treatment relapse samples from multiple genotype 3 HCV infected subjects in the Phase 3 clinical studies. No shift in the phenotypic susceptibility to sofosbuvir or ribavirin of subject isolates with these substitutions was detected. In addition, S282R and L320F substitutions were detected on treatment by deep sequencing in a pre-transplant subject with a partial treatment response. The clinical significance of these findings is unknown.

Effect of baseline HCV polymorphisms on treatment outcome
Baseline NS5B sequences were obtained for 1,292 subjects from Phase 3 studies by population sequencing and the S282T substitution was not detected No statistically significant association was observed between the presence of any HCV NS5B variant at baseline and treatment outcome.

Paediatric population

Baseline NS5B sequences were obtained for 47 patients in the Phase 2 study. Among these, one patient was found to have a NS5B RAV substitution (F289L). This patient achieved SVR12.

Cross-resistance

HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were fully susceptible to other classes of anti-HCV agents. 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 inhibitors, NS3 protease inhibitors and NS5A inhibitors.

Clinical efficacy and safety

The efficacy of sofosbuvir was evaluated in five Phase 3 studies in a total of 1,568 subjects with genotypes 1 to 6 chronic hepatitis C. One study was conducted in treatment-naïve subjects with genotype 1, 4, 5 or 6 chronic hepatitis C in combination with peginterferon alfa 2a and ribavirin and the other four studies were conducted in subjects with genotype 2 or 3 chronic hepatitis C in combination with ribavirin including one in treatment-naïve subjects, one in interferon intolerant, ineligible or unwilling subjects, one in subjects previously treated with an interferon-based regimen, and one in all subjects irrespective of prior treatment history or ability to receive treatment with interferon. Subjects in these studies had compensated liver disease including cirrhosis. Sofosbuvir was administered at a dose of 400 mg once daily. The ribavirin dose was weight-based at 1,000-1,200 mg daily administered in two divided doses, and the peginterferon alfa 2a dose, where applicable, was 180 µg per week. Treatment duration was fixed in each study.

Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate for all studies which was defined as HCV RNA less than lower limit of quantification of the assay (i.e. 25 IU/ml) at 12 weeks after the end of treatment (SVR12).

More than 50% of the participants in each study had a baseline HCV RNA level > 6 $\log_{10}$ IU/ml.

Further details of these studies are provided in Table 5 below.

For information on studies of direct- acting antivirals against CHC that are used in combination with sofosbuvir, e.g. daclatasvir, refer to the summary of product characteristics of these products.

Table 5: Key design/study population characteristics and main results of the phase 3 studies of sofosbuvir

Population; Study design	**Study Arms (number of subjects treated)**	**Response rates (SVR12)**	**Subgroup Analyses**	**Further analyses**
Treatment naïve (TN) (GT1, 4, 5 or 6); Single-arm, open-label	SOF+Peg-IFN alfa+RBV 12 weeks (327; 17% Black, 14% Hispanic/Latino)	Overall: 91%	Genotype 1: 90% (262/292) Genotype 4,5,6: 97% (34/35) Cirrhosis N/Y: 93% (253/273)/ 80% (43/54) Race: Black: 87% Non-Black: 91%	Outcome for subjects without SVR12 On-treatment virologic failure: 0 % Relapse[a]: 9% Other[b]: 1%
TN (GT2 or 3); randomised, open-label, active-controlled	SOF +RBV 12 Weeks (256) Peg-IFN alfa+RBV 24 weeks (243) [3% Black, 14% Hispanic/Latino]	SOF+RBV / PEG+RBV 67% / 67% GT2 95% / GT2 78% GT3 56% / GT3 63%	GT2 (140) / GT3 (359) Cirrhosis (in 20% of the participants) SOF+RBV / PEG+RBV / SOF+RBV[c] / PEG+RBV N 97% / N 81% / N 61% / N 71% Y 83% / Y 62% / Y 34% / Y 30%	Outcome for subjects without SVR12 SOF+RBV[c] / PEG+RBV On-treatment virologic failure <1% / 7% Relapse[a]: 30% / 21% Other[b] 3% / 7%
Interferon intolerant, ineligible or unwilling subjects (GT2 or 3), randomised, double-blind, placebo-controlled	SOF +RBV 12 Weeks (207) Placebo 12 weeks (71) [5% Black, 11% Hispanic/Latino]	SOF+RBV / Placebo 78% / 0% GT2 93% / GT2 0% GT3 61% / GT3 0%	SOF+RBV GT2 (143) / GT3 (135) Cirrhosis (in 16% of the participants) No 92% 68% Yes 94% 21% Interferon classification Ineligible (88) 88% 70% Intolerant (17) 100% 50% Unwilling 102) 95% 53%	Outcome for subjects without SVR12 SOF+RBV / Placebo On-treatment virologic failure 0% / 97% Relapse[a] 20% / 0% Other[b] 2% / 3%
Previous interferon relapsers or nonresponders (GT2 or 3), randomised, double-blind	SOF +RBV 12 Weeks (103) SOF +RBV 16 Weeks (98) [3% Black, 9% Hispanic/Latino]	SOF+RBV 12w / SOF+RBV 16w 50% / 71% GT2 82% / GT2 89% GT3 30% / GT3 62%	GT2 / GT3 SOF+RBV 12w / SOF+RBV 16w / SOF+RBV 12w / SOF+RBV 16w Cirrhosis (in 34% of the participants) N 90% / N 92% / N 37% / N 63% Y60% / Y 78% / Y 19% / Y 61% Response to prior HCV treatment (75% of the participants were prior relapsers) Rel 86% / Rel 89% / Rel 31% / Rel 65% NR 70% / NR 88% / NR 27% / NR 53%	Outcome for subjects without SVR12 SOF+RBV 12w[d] / SOF+RBV 16w[d] On-treatment virologic failure 0% / 0% Relapse[a] 48% / 29% Other[b] 3% / 0%
TN or previous interferon relapsers (65%) or nonresponders (GT2 or 3), open-label	SOF +RBV 12 Weeks for GT2 (73) SOF +RBV 12 Weeks for GT3 (11) SOF +RBV 24 Weeks for GT3 (250) Placebo 12 weeks (85) [	GT2 12w / GT3 12w / GT3 16w 93% / 27% / 84%	GT2 SOF +RBV 12w (73) / GT3 SOF +RBV 24w (250) TN 97% / TN 93% Cirrhosis N 97% / N 93% Y 100% (2/2) / Y 92% TE 90% / TE 77% Cirrhosis (in 21% of the participants) N 91% / N 85% Y 88% / Y 60%	Outcome for subjects without SVR12 GT2 12w / GT3 12w / GT3 16w On-treatment virologic failure 9% / 0% / 0.4% Relapse[a] 7% / 55% / 14% Other[b] 0% / 18% / 2%
HCV/HIV-1	SOF +RBV	GT2/ / GT2/ / GT1	GT2 / GT3	Outcome for subjects without

coinfected TN (GT1) • HCV/HIV-1 coinfected TN or previous interferon relapsers or nonresponders (GT2 or 3), Open-label, 95% on ART	24 Weeks for GT1 (114) SOF +RBV 12 Weeks for GT2 or 3 TN (68) SOF +RBV 24 Weeks for GT2 or 3 previous interferon relapsers or nonresponders (41)	3 TN SOF+ RBV 12w (68)	3 TE SOF+ RBV 24w (28)	TN SOF+ RBV 24w (114)					SVR12			
					SOF+RBV TN 12 w	SOF+RBV TE 24w	SOF+RBV TN 12w	SOF+RBV TE 24w	GT2/3 TN SOF+RBV 12w	GT2/3 TE SOF+RBV 24w	GT1 TN SOF+RBV 24w	
					88%	93%	67%	92%	On-treatment virologic failure			
									1%	0%	76%	
		75%	93%	76%	Cirrhosis (in 15% of the participants)				Relapse[a]			
					N 88%	N 92%	N 67%	N 100% (8/8)	18%	7%	22%	
					Y 100% (1/1)	Y 100% (2/2)	Y 67%	Y 80%	Other[b]			
									6%	0%	1%	

GT: genotype, Y: yes, N: no; TN: treatment naïve; TE: treatment experienced, Rel: relapsers; NR: non-responders
a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).
c. The efficacy analysis includes 3 patients with recombinant genotype 2/1 HCV infection.
d. The efficacy analysis includes 6 patients with recombinant genotype 2/1 HCV infection.

Patients awaiting liver transplantation - Study 2025
Sofosbuvir was studied in HCV infected subjects, regardless of genotype with hepatocellular carcinoma (HCC), prior to undergoing liver transplantation in an open-label clinical study evaluating the safety and efficacy of sofosbuvir 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).
An interim analysis was conducted on 61 subjects, of whom 44 subjects underwent liver transplantation following up to 48 weeks of treatment with sofosbuvir and ribavirin; 41 had HCV RNA <LLOQ at the time of transplantation. The virologic response rates of the subjects transplanted with HCV RNA <LLOQ was 62% (23/37) at 12 weeks post-transplant. 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.

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

Liver transplant recipients - Study 0126
Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 24 weeks of treatment with sofosbuvir and ribavirin in patients with chronic hepatitis C, who had undergone liver transplantation 6 to 150 months prior to screening.
Forty subjects (33 with HCV genotype 1 infection, 6 with HCV genotype 3 infection, and 1 with HCV genotype 4 infection) were enrolled, 35 of whom had previously failed interferon-based treatment, and 16 of whom had cirrhosis. 28 out of 40 (70%) subjects achieved SVR12: 22/33 (73%) with HCV genotype 1 infection, 6/6 (100%) with HCV genotype 3 infection, and 0/1 (0%) with HCV genotype 4 infection. All subjects who achieved SVR12 achieved SVR24 and SVR48.

Paediatric population
The efficacy of sofosbuvir in HCV-infected paediatric subjects 12 years of age and older was evaluated in 50 subjects with HCV genotype 2 (N = 13) or genotype 3 (N = 37) in a Phase 2, open label clinical trial. Subjects with HCV genotype 2 or 3 infection in the trial were treated with sofosbuvir and weight-based ribavirin for 12 or 24 weeks, respectively (see section 4.2).
Of the 50 treated subjects, the median age was 15 years (range: 12 to 17); 42% of the subjects were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 61 kg (range: 30 to 101 kg); 18% were treatment experienced; 66% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL and no subjects had known cirrhosis. The majority of subjects (69%) had been infected through vertical transmission. The SVR12 rate was 100% (13/13) in genotype

2 subjects and 97% (36/37) in genotype 3 subjects. No subject experienced on-treatment virologic failure or relapse.

5.2 Pharmacokinetic properties

Sofosbuvir is a nucleotide prodrug that is extensively metabolised. The active metabolite is formed in hepatocytes and not observed in plasma. The predominant (>90%) metabolite, GS-331007, is inactive. It is formed through sequential and parallel pathways to the formation of active metabolite.

Absorption

The pharmacokinetic properties of sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C.
Based on population pharmacokinetic analysis in subjects with genotypes 1 to 6 HCV infection (n = 986), steady-state AUC_{0-24} for sofosbuvir and GS-331007 was 1,010 ng•h/mL and 7,200 ng•h/mL, respectively. Relative to healthy subjects (n = 284), the sofosbuvir and GS-331007 AUC_{0-24} was 57% higher and 39% lower, respectively in HCV infected subjects.

Following single dose of administration of Sofosbuvir Tablets, Film-coated 400 mg in healthy volunteers, mean (± SD) sofosbuvir C_{max} value was 1287 (± 572) ng/ml and the corresponding value for AUC_{0-t} was 1503
(±415) ng·hour/ml. The mean sofosbuvir t_{max} value was 1.53 ± 0.67 hours.

Effects of food
Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold, with little effect on peak concentration. The exposure to GS-331007 was not altered in the presence of a high-fat meal.

Distribution

Sofosbuvir is not a substrate for hepatic uptake transporters, organic anion-transporting polypeptide (OATP) 1B1 or 1B3, and organic cation transporter (OCT) 1. While subject to active tubular secretion, GS-331007 is not a substrate for renal transporters including organic anion transporter (OAT) 1 or 3, OCT2, MRP2, P-gp, BCRP or MATE1. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1. GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Sofosbuvir is approximately 85% bound to human plasma proteins (*ex vivo* data) and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Biotransformation

Sofosbuvir is extensively metabolised 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 catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. Sofosbuvir and GS-331007 are not substrates or inhibitors of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes.

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.

Elimination

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 with a large part actively secreted. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

Linearity/non-linearity

The dose linearity of sofosbuvir and its primary metabolite, GS-331007, was evaluated in fasted healthy subjects. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 400 mg.

Pharmacokinetics in special populations

Gender and race

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

Elderly

Population pharmacokinetic analysis in HCV infected subjects 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. Clinical studies of sofosbuvir included 65 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.

Renal impairment

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR ≥50 and <80 mL/min/1.73 m^2), moderate (eGFR ≥30 and <50 mL/min/1.73 m^2), severe renal impairment (eGFR <30 mL/min/1.73 m^2) and subjects with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR >80 mL/min/1.73 m^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 subjects with ESRD, relative to subjects with normal renal function, sofosbuvir $AUC_{0\text{-inf}}$ was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when sofosbuvir was dosed 1 hour after haemodialysis. The $AUC_{0\text{-inf}}$ of GS-331007 in subjects with ESRD could not be reliably determined. However, data indicate at least 10-fold and 20-fold higher exposure to GS-331007 in ESRD compared to normal subjects when sofosbuvir was administered 1 hour before or 1 hour after haemodialysis, respectively.

Haemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007. A 4-hour haemodialysis session removed approximately 18% of administered dose. No dose adjustment is required for patients with mild or moderate renal impairment. The safety of sofosbuvir has not been assessed in patients with severe renal impairment or ESRD (see section 4.4).

Hepatic impairment

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV infected subjects with moderate and severe hepatic impairment (CPT class B and C). Relative to subjects 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 subjects indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007. No dose adjustment of

sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment (see section 4.2).

Paediatric population
Sofosbuvir and GS-331007 exposures in adolescents aged 12 to <18 years were similar to those in adults from Phase 2/3 studies following administration of sofosbuvir (400 mg). The pharmacokinetics of sofosbuvir and GS-331007 have not been established in paediatric patients < 12 years of age.

Pharmacokinetic/pharmacodynamic relationship(s)
Efficacy, in terms of rapid virologic response, has been shown to correlate with exposure to sofosbuvir as well as GS 331007. However, neither of these entities has been evidenced to be a general surrogate marker for efficacy (SVR12) at the therapeutic 400 mg dose.

5.3 Preclinical safety data

In repeat dose toxicology studies in rat and dog, high doses of the 1:1 diastereomeric mixture caused adverse liver (dog) and heart (rat) effects and gastrointestinal reactions (dog). Exposure to sofosbuvir in rodent studies could not be detected likely due to high esterase activity; however, exposure to the major metabolite GS-331007 at the adverse dose was 29 times (rat) and 123 times (dog) higher than the clinical exposure at 400 mg sofosbuvir. No liver or heart findings were observed in chronic toxicity studies at exposures 9 times (rat) and 27 times (dog) higher than the clinical exposure.

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.

Sofosbuvir had no effects on embryo-foetal viability or on fertility in rat and was not teratogenic in rat and rabbit development studies. No adverse effects on behaviour, reproduction or development of offspring in rat were reported. In rabbit studies exposure to sofosbuvir was 9 times the expected clinical exposure. In the rat studies, exposure to sofosbuvir could not be determined but exposure margins based on the major human metabolite ranged from 8 to 28 times higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir-derived material was transferred through the placenta in pregnant rats and into the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate

Film coat: polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide yellow, iron oxide red, ferrosoferric oxide/black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months (White bottle; HDPE)
36 months (Blue bottle; HDPE)

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

White coloured high density polyethylene (HDPE) bottles with a white polypropylene screw cap containing 28 film-coated tablets with a canister containing silica gel desiccant.

Blue coloured high density polyethylene (HDPE) bottles with a blue polypropylene screw cap containing 28 film-coated tablets with a canister containing silica gel desiccant.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

HP001

9. DATE OF FIRST PREQUALIFICATION

20 July 2017

10. DATE OF REVISION OF THE TEXT

July 2018
Section 6 was updated in April 2020

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/

Reference list:

European SmPC Sovaldi, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf

US- full prescribing information Sovaldi, revised 11/2017, available at
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204671s012lbl.pdf
Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection.
Updated version April 2016, available at:
http://apps.who.int/iris/bitstream/handle/10665/205035/9789241549615_eng.pdf;jsessionid=F890AC78D569AB632C49293BFC910732?sequence=1

University of Liverpool, HEP drug interactions, available at *:* https://www.hep-druginteractions.org/checker

All weblinks were last accessed 21 May 2018