WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HP002 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg sofosbuvir.

Excipients with potential clinical effect

Each film-coated tablet contains 3.24mg of FD&C yellow #6/sunset yellow FCF aluminium lake.

3. PHARMACEUTICAL FORM

Film-coated tablets

Orange, oval, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have 'H' debossed (stamped into) one side and 'S14' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HP002 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults and children (see section 4.2).

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Treatment with [HP002 trade name] should be initiated and monitored by a health care provider experienced in the management of patients with chronic hepatitis C.

[HP002 trade name] should be used in combination with other medicines for hepatitis C.

Posology

[HP002 trade name] is taken once daily by mouth. The recommended dose depends on body weight and the medicinal product it is taken with, as follows:

Body weight	**Dose and duration of [HP002 trade name]**	**Daily dose of sofosbuvir**
Use with daclatasvir[1]		
26 kg or more	1 tablet per day for 12 weeks[2]	400 mg
14 kg to less than 26 kg	*use alternative formulation*	*200 mg*
Use with velpatasvir[1]		
30 kg or more	1 tablet per day for 12 weeks	400 mg
17 kg to less than 30 kg	*use alternative formulation*	*200 mg*
Use with ledipasvir[3]		
35 kg or more	1 tablet per day for 12 weeks	400 mg
17 kg to less than 35 kg	*use alternative formulation*	*200 mg*

[1] For use in all genotypes.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

[2] Treatment for 24 weeks is recommended in those who are treatment experienced or who have compensated cirrhosis. It may also be considered in settings where genotype 3 is known to be highly prevalent (>10%).

[3] For use in those with genotype 1, 4, 5, or 6 infection or where genotype 3 infection is uncommon.

Missed doses and vomiting after a dose

Patients should be instructed that, if they miss a dose of [HP002 trade name], the dose should be taken as soon as possible if remembered within 18 hours of the scheduled dose time. However, if the missed dose is remembered more than 18 hours after the scheduled dose, the dose should be skipped, and the next dose taken at the appropriate time.

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.

Discontinuation of dosing

If the other hepatitis C medicines used in combination with sofosbuvir are permanently discontinued, sofosbuvir should also be discontinued.

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.

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) or end stage renal disease (ESRD) requiring haemodialysis. [HP002 trade name] can be used in these patients with no dose adjustment when no other relevant treatment options are available (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.

Method of administration

[HP002 trade name] is taken orally with food. Patients should be instructed to swallow the tablet whole. The tablet should not be chewed or crushed, due to the bitter taste of the active substance.

4.3 Contraindications

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

Use with strong P-gp inducers

[HP002 trade name] should not be given with medicinal products that are strong P-glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort (*Hypericum perforatum*)). Co-administration will significantly decrease sofosbuvir plasma concentration and could result in loss of efficacy of [HP002 trade name] (see section 4.5).

4.4 Special warnings and precautions for use

General

[HP002 trade name] is 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, [HP002 trade name] should also be discontinued.

Consult the summary of product characteristics for co-prescribed medicinal products before starting therapy with [HP002 trade name].

Severe bradycardia and heart block

Cases of severe bradycardia and heart block have been observed when sofosbuvir in combination with another direct-acting antiviral (DAAs, including daclatasvir and ledipasvir) was used in patients taking concomitant amiodarone (with or without other drugs that lower heart rate). Bradycardia has generally occurred within hours to days, but cases with a longer time to onset have been observed mostly up to 2 weeks after initiating HCV treatment. The mechanism is not established.

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 co-administration 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 in patients who have discontinued amiodarone within the past few months and are starting 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.

Co-administration with other direct-acting antivirals against HCV

There are no data to support the co-administration of sofosbuvir and boceprevir or telapravir. Such co-administration is not recommended (see also section 4.5).

Use with moderate P-gp inducers

Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentration leading to a reduced therapeutic effect. Co-administration of such medicinal products is not recommended with [HP002 trade name] (see section 4.5).

Use in patients with diabetes

Patients with diabetes may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The health care provider in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is started.

Renal impairment

Safety data are limited in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or ESRD requiring haemodialysis. [HP002 trade name] can be used in these patients with no dose adjustment when no other relevant treatment options are available (see sections 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.

Excipients

[HP002 trade name] contains FD&C yellow #6/sunset yellow FCF aluminium lake and may cause allergic reactions.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Sofosbuvir is a prodrug that undergoes extensive metabolism, mostly to inactive metabolites such as GS-331007, which accounts for more than 90% of the exposure after a dose. The parent drug is converted intracellularly to the pharmacologically active form (for further information see section 5.2).

Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not.

Medicinal products that are strong P-gp *inducers* in the intestine (rifampicin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may significantly decrease sofosbuvir plasma concentration leading to a reduced therapeutic effect of [HP002 trade name] and thus are contraindicated with sofosbuvir (see section 4.3).

Medicinal products that are moderate P-gp inducers in the intestine (e.g. modafinil, oxcarbazepine and rifapentine) may decrease sofosbuvir plasma concentrations leading to reduced therapeutic effect of [HP002 trade name]. 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.

Impact of DAA therapy on drugs metabolized by the liver

The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV.

Other interactions

Drug interaction information for sofosbuvir with potential concomitant medicinal products is summarised in the table 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.

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 [HP002 trade name]**
ANALEPTICS		

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 [HP002 trade name]**
Modafinil	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	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	Effect on amiodarone and sofosbuvir concentrations unknown.	Co-administration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia (see sections 4.4 and 4.8). Use only if no other alternative is available. Close monitoring is required in such a case.
ANTICOAGULANTS		
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		
Phenobarbital Phenytoin	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Sofosbuvir is contraindicated with phenobarbital and phenytoin, which are potent intestinal P-gp inducers (see section 4.3).
Carbamazepine	*Sofosbuvir* ↓ C_{max} 0.52 (0.43, 0.62) ↓ AUC 0.52 (0.46, 0.59) C_{min} (NA) *GS-331007* ↔ C_{max} 1.04 (0.97, 1.11) ↔ AUC 0.99 (0.94, 1.04) C_{min} (NA) (Induction of P-gp)	Sofosbuvir is contraindicated with carbamazepine, a potent intestinal P-gp inducer (see section 4.3).
Oxcarbazepine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	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		

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 [HP002 trade name]**
Rifampicin[f] (600 mg SD)	*Sofosbuvir* ↓ C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) C_{min} (NA) *GS-331007* ↔ C_{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) C_{min} (NA) (Induction of P-gp)	Sofosbuvir is contraindicated with rifampicin, a potent intestinal P-gp inducer (see section 4.3).
Rifabutin	*Sofosbuvir* ↓ C_{max} 0.64 (0.53, 0.77) ↓ AUC 0.76 (0.63, 0.91) C_{min} (NA) *GS-331007* ↔ C_{max} 1.15 (1.03, 1.27) ↔ AUC 1.03 (0.95, 1.12) C_{min} (NA) (Induction of P-gp)	No dose adjustment of sofosbuvir is required when concomitantly used with rifabutin.
Rifapentine	Interaction not studied. *Expected:* ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	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.
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) Telaprevir (TPV)	Interaction not studied. *Expected:* ↑ Sofosbuvir (TPV) ↔ Sofosbuvir (BOC) ↔ GS-331007 (TPV or BOC)	No drug-drug interaction data exists regarding the co-administration of sofosbuvir with boceprevir or telaprevir.
NARCOTIC ANALGESICS		

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 [HP002 trade name]**
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 at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
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 at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		

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 [HP002 trade name]**
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[f] (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.
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[f] (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		

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 [HP002 trade name]**
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.
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		
Raltegravir[f] (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) C_{min} (NA)	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 Fertility, pregnancy and breastfeeding

Women of childbearing potential / contraception in males and females

Women of childbearing age may be offered pregnancy testing and should be informed about the lack of available data on the safety and efficacy of sofosbuvir during pregnancy.

Since sofosbuvir must be taken in combination with other hepatitis C medicinal products, the contraindications and warnings for those medicinal products are applicable.

Pregnancy

There are 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 fetal 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.

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

[HP002 trade name] has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Sofosbuvir has been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. In general, direct acting antivirals (DAAs) such as sofosbuvir are well tolerated by persons with HCV infection, with only minor side-effects.

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with sofosbuvir in combination with ribavirin. The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10), and uncommon (1 in 1000 to 1 in 100).

Infections and infestations

Common	nasopharyngitis

Blood and lymphatic system disorders

Very common	haemoglobin decreased
Common	anaemia

Metabolism and nutrition disorders

Common	decreased appetite

Psychiatric disorders

Very common	insomnia
Common	depression

Nervous system disorders

Very common	headache
Common	disturbance in attention

Respiratory, thoracic and mediastinal disorders

Common	dyspnoea, dyspnoea exertional, cough

Gastrointestinal disorders

Very common	nausea
Common	abdominal discomfort, constipation, dyspepsia

Hepatobiliary disorders

Very common	Blood bilirubin increased

Skin and subcutaneous tissue disorders

Common	alopecia, pruritus, dry skin

Musculoskeletal and connective tissue disorders

Common	arthralgia, back pain, muscle spasms, myalgia

General disorders

Very common	fatigue, irritability
Common	pyrexia, asthenia

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.

Patients with renal impairment

Sofosbuvir in a fixed dose combination with ledipasvir was administered for 12 weeks to 18 patients with genotype 1 CHC and severe renal impairment in an open-label study (Study 0154). The safety of sofosbuvir

in a fixed dose combination with either ledipasvir or velpatasvir has been studied in 154 patients with end stage renal disease (ESRD) requiring dialysis (Study 4062 and Study 4063). In this setting, exposure of sofosbuvir metabolite GS-331007 is 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients.

Paediatric population

The safety and efficacy of sofosbuvir in paediatric patients aged 3 years and above are based on data from 106 patients who were treated with sofosbuvir and ribavirin for 12 weeks (genotype 2 patients) and for 24 weeks (genotype 3 patients) in a Phase 2, open-label clinical trial. No adverse drug reactions specific to sofosbuvir were identified. The adverse reactions observed were generally consistent with those observed in clinical studies of sofosbuvir plus ribavirin in adults. Decreased appetite was observed as a very common adverse drug reaction to sofosbuvir when given in combination with ribavirin oral solution in paediatric patients aged 3 to < 12 years.

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).

Skin disorders

Frequency not known: Stevens-Johnson syndrome.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

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: J05AP08

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 is neither an inhibitor of

human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Resistance

In cell culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, 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

The presence of NS5B RAVs did not impact treatment outcome; all patients with baseline NS5B nucleoside inhibitor RAVs achieved SVR following treatment with sofosbuvir.

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 the table 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.

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	GT2 (140)		GT3 (359)		Outcome for subjects without SVR12	
		67%	67%	Cirrhosis (in 20% of the participants)				SOF+ RBV[c]	PEG+ RBV
		GT2 95%	GT2 78%	SOF+ RBV	PEG+ RBV	SOF+ RBV[c]	PEG+ RBV	On-treatment virologic failure	
		GT3 56%	GT3 63%	No 97%	No 81%	No 61%	No 71%	<1%	7%
								Relapse[a]:	
				Yes 83%	Yes 62%	Yes 34%	Yes 30%	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	SOF+RBV				Outcome for subjects without SVR12	
				GT2 (143)		GT3 (135)			
				Cirrhosis (in 16% of the participants)				SOF+RBV	Placebo
		78%	0%	No 92%		No 68%		On-treatment virologic failure	
				Yes 94%		Yes 21%		0%	97%
		GT2	GT2	Interferon classification				Relapse[a]	

		93%	0%	Ineligible 88%	Ineligible 70%	20%	0%
		GT3 61%	GT3 0%	Intolerant 100%	Intolerant 50%	Other[b]	
				Unwilling 95%	Unwilling 53%	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[d]	SOF+ RBV 16w[d]	GT2	GT3	Outcome for subjects without SVR12	
				SOF+ RBV 12w / SOF+ RBV 16w	SOF+ RBV 12w / SOF+ RBV 16w	SOF+RBV 12w[d]	SOF+RBV 16w[d]
		50%	71%	Cirrhosis (in 34% of the participants)		On-treatment virologic failure	
				No 90% / No 92%	No 37% / No 63%	0%	0%
		GT2 82%	GT2 89%	Yes 60% / Yes 78%	Yes 19% / Yes 61%	Relapse[a]	
				Response to prior HCV treatment (75% of the participants were prior relapsers)		48%	29%
		GT3 30%	GT3 62%	Rel 86% / Rel 89%	Rel 31% / Rel 65%	Other[b]	
				NR 70% / NR 88%	NR 27% / NR 53%	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)	GT2 12w	GT3 12w	GT3 24w	GT2 SOF +RBV 12w (73)	GT3 SOF +RBV 24w (250)	Outcome for subjects without SVR12
					TN 97%	TN 93%	GT2 12w / GT3 12w / GT3 24w
					Cirrhosis		
					No 97%	No 93%	
					Yes 100% (2/2)	Yes 92%	On-treatment virologic failure
		93%	27%	84%	TE 90%	TE 77%	9% / 0% / 0.4%
					Cirrhosis (in 21% of the participants)		Relapse[a]
					No 91%	No 85%	7% / 55% / 14%
					Yes 88%	Yes 60%	Other[b]
							0% / 18% / 2%
HCV/HIV-1	SOF +RBV	GT2	GT2	GT1	GT2	GT3	Outcome for subjects

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 (28)	/3 TN SOF +RBV 12w (68)	/3 TE SOF +RBV 24w (28)	TN SOF +RBV 24w (114)					without 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%	1%
		75%	93%	76%	Cirrhosis (in 15% of the participants)				Relapse[a]		
					No 88%	No 92%	No 67%	No 100% (8/8)	18%	7%	22%
					Yes 100% (1/1)	Yes 100% (2/2)	Yes 67%	Yes 80%	Other[b]		
									6%	0%	1%

GT: genotype, 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 who 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 3 years of age and older was evaluated in 106 subjects with HCV genotype 2 (N = 31) or genotype 3 (N = 75) 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.

Patients aged 12 to < 18 Years:

Sofosbuvir was evaluated in 52 patients 12 to < 18 years with genotype 2 (n = 13) or genotype 3 (n = 39) HCV infection. The median age was 15 years (range: 12 to 17); 40% of the patients were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino; mean weight was 60.4 kg (range: 29.6 to 75.6 kg); 17% were treatment experienced; 65% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no patients had known cirrhosis. The majority of patients (69%) had been infected through vertical transmission.

The SVR12 rate was 98% overall (100% [13/13] in genotype 2 patients and 97% [38/39]) in genotype 3 patients). No patient experienced on-treatment virologic failure or relapse; one patient with genotype 3 HCV infection achieved SVR4 but did not return for the SVR12 visit.

Patients aged 6 to < 12 Years:

Sofosbuvir was evaluated in 41 patients 6 to < 12 years of age with genotype 2 (n = 13), or genotype 3 (n = 28) HCV infection. The median age was 9 years (range: 6 to 11); 73% of the patients were female; 71% were White and 20% were Asian; 15% were Hispanic/Latino; mean weight was 33.7 kg (range: 15.1 to 80.0 kg); 98% were treatment naive; 46% had baseline HCV RNA levels greater than or equal to 800,000 IU /mL; and no patients had known cirrhosis. The majority of patients (98%) had been infected through vertical transmission.

The SVR12 rate was 100% (100% [13/13] in genotype 2 patients and 100% [28/28] in genotype 3 patients). No patients experienced on-treatment virologic failure or relapse.

Patients aged 3 to < 6 Years:

Sofosbuvir was evaluated in 13 patients 3 to < 6 years with genotype 2 (n = 5) or genotype 3 (n = 8) HCV infection. The median age was 4 years (range: 3 to 5); 77% of the patients were female; 69% were White, 8% were Black, and 8% were Asian; 8% were Hispanic/Latino; mean weight was 16.8 kg (range: 13.0 to 19.2 kg); 100% were treatment naive; 23% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no patients had known cirrhosis. The majority of patients (85%) had been infected through vertical transmission.

The SVR12 rate was 92% overall (80% [4/5] in genotype 2 patients and 100% [8/8] in genotype 3 patients). No patients experienced on-treatment virologic failure or relapse; one patient with genotype 2 HCV prematurely discontinued study treatment after 3 days due to abnormal taste of the medication and did not return for post-treatment Week 12.

5.2 Pharmacokinetic properties

The absorption characteristics of [HP002 trade name] have been determined after administration of one tablet (1) in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* ± standard deviation**
Maximum concentration (C_{max}) ng/mL	1116 ± 546
Area under the curve (AUC_{0-inf}), a measure of the extent of absorption ng·hour/mL	1492 ± 424
Time to attain maximum concentration (t_{max}) hours	1.75 ± 0.63

*arithmetic mean

Pharmacokinetics of sofosbuvir

<table>
<tr><th></th><th>Sofosbuvir</th></tr>
<tr><td colspan="2">General</td></tr>
<tr><td></td><td>Sofosbuvir is a nucleotide prodrug. .After oral administration, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic and intestinal metabolism.

The predominant inactive circulating metabolite GS-331007 accounts for greater than 90% of drug-related material systemic exposure. The parent sofosbuvir accounts for approximately 4% of drug-related material systemic exposure.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Absolute bioavailability</td><td>Vc 197 L</td></tr>
<tr><td>Oral bioavailability</td><td>At least 82.5%
T_{max} 1 hr</td></tr>
<tr><td>Food effect</td><td><table><tr><td></td><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</td></tr><tr><td>High fat:</td><td>78%↑</td><td>↔</td><td>↓</td></tr></table></td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>NA</td></tr>
<tr><td>Plasma protein binding in vitro</td><td>85% (ex vivo data)

Binding is independent of drug concentration over the range of 1 to 20 μg/mL.</td></tr>
<tr><td>Tissue distribution</td><td>No human data available. 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.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td></td><td>The active triphosphate metabolite GS-461203 is formed in the liver by extensive metabolism via sequential hydrolysis (Cat A or CES1) and phosphoramidate cleavage (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of the inactive nucleoside metabolite GS-331007.

Sofosbuvir and GS-331007 are not substrates of UGT1A1 or CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzymes.</td></tr>
<tr><td>Active metabolite(s)</td><td>The active metabolite GS-461203 is formed in hepatocytes and not observed in plasma.</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Elimination half life</td><td>Sofosbuvir 0.4 hours</td></tr>
<tr><td>Mean systemic clearance (Cl/F)</td><td>NA</td></tr>
<tr><td>% of dose excreted in urine</td><td>80%
(3.5% as sofosbuvir)</td></tr>
<tr><td>% of dose excreted in faeces</td><td>14%</td></tr>
</table>

Pharmacokinetic linearity	AUC is near dose proportional over the dose range of 200 mg to 400 mg (in fasted healthy subjects)
Drug interactions *(in vitro*)	
Transporters	Sofosbuvir is a substrate of P-gp and BCRP
Enzymes	Sofosbuvir is a substrate for CatA and CES1, followed by HINT1, however no interaction in vivo is expected involving this pathway.

NA = Information not available

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 1.6-fold, 2.1-fold and 2.7-fold higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 1.6-fold, 1.9-fold and 5.5-fold higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir $AUC_{0\text{-}inf}$ was 1.3-fold higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 1.6-fold 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.

The pharmacokinetics of sofosbuvir, and GS-331007 were studied in HCV-infected adult patients with ESRD requiring dialysis treated with ledipasvir/sofosbuvir (n = 94) for 8, 12, or 24 weeks or sofosbuvir/velpatasvir (n = 59) for 12 weeks, and compared to patients without renal impairment in the ledipasvir/sofosbuvir and sofosbuvir/velpatasvir Phase 2/3 trials (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 paediatric patients aged 3 years and above were similar to those in adults from Phase 2/3 studies following administration of sofosbuvir.

The pharmacokinetics of sofosbuvir and GS-331007 have not been established in paediatric patients aged < 3 years (see section 4.2).

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-fetal 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 partially hydrolysed
Macrogol/polyethylene glycol
Talc
Titanium dioxide
FD&C yellow #6/ sunset yellow FCF aluminium lake

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

HDPE bottles

Plastic (HDPE) bottle containing 14 or 28 tablets. It also contains a sachet of desiccant (drying material) and a polyester coil to keep the tablets in place. The bottle has a childproof plastic (polypropylene) screw cap with a pulp (cardboard-type material) liner.

Blister packs

Aluminium foil on aluminium foil blister cards, each containing 10 tablets. Available in cartons of 10 x 10 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

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

7. SUPPLIER

Hetero Labs Limited,
7-2-A2, Hetero Corporate,
Industrial Estates,
Sanath Nagar, Hyderabad-500 018.
Telangana, India.

8. Tel: +91 40 23704923WHO REFERENCE NUMBER (WHO Prequalification Programme)

HP002

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07 February 2018

10. DATE OF REVISION OF THE TEXT

March 2024

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Section 4.5

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http://www.hep-druginteractions.org

http://www.hiv-druginteractions.org

[All links accessed in March 2024]

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products