# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

MYHEP 400 mg
(Sofosbuvir Tablets 400 mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablets contains-:
Sofosbuvir.…400 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Peach colored, capsule shaped, biconvex, beveled edge film-coated tablets debossed with "**SF400**" onone side of the tablet and "**M**" on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Sofosbuvir 400 mg film-coated tablets is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults (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 400 mg film-coated tablets treatment should be initiated and monitored by a physician 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 400 mg film-coated tablets should be used in combination with other medicinal products. Monotherapy of Sofosbuvir 400 mg film-coated tablets is not recommended (see section 5.1). Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Sofosbuvir 400 mg film-coated tablets. The recommended co-administered medicinal product(s) and treatment duration for Sofosbuvir 400 mg film-coated tablets combination therapy are provided inTable 1.

**Table 1: Recommended co-administered medicinal product(s) and treatment duration for Sofosbuvir 400 mg film-coated tablets combination therapy**

| Patient population * | Treatment | Duration |
|---|---|---|
| Patients with genotype 1, 4, 5 or 6 CHC | Sofosbuvir 400 mg film-coated tablets + ribavirin + peginterferon alfa | 12 weeks[a,b] |
| | Sofosbuvir 400 mg film-coated tablets + ribavirin<br><br>Only for use in patients ineligible or intolerant to peginterferon alfa (see section 4.4) | 24 weeks |
| Patients | Sofosbuvir 400 mg film-coated tablets + ribavirin | 12 weeks[b] |
| Patients | Sofosbuvir 400 mg film-coated tablets + ribavirin + peginterferon alfa | 12 weeks[b] |
| | Sofosbuvir 400 mg film-coated tablets + ribavirin | 24 weeks |
| Patients with CHC awaiting liver transplantation | Sofosbuvir 400 mg film-coated tablets + 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 400 mg film- coated tablets, 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 400 mg film-coated tablets is weight- based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg) and

administered orally in two divided doses withfood.

Concerning co-administration with other direct-acting antivirals against HCV, see section 4.4.

*Dose modification*
Dose reduction of Sofosbuvir 400 mg film-coated tablets 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 400 mg film-coated tablets**

| **Laboratory values** | **Reduce ribavirin dose to 600mg/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 atreduced 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 to1,200 mg daily).

*Discontinuation of dosing*
If the other medicinal products used in combination with Sofosbuvir 400 mg film-coated tablets are permanently discontinued, Sofosbuvir 400 mg film-coated tablets 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 400 mg film-coated tablets is required for patients with mild or moderate renal impairment. The safety and appropriate dose of Sofosbuvir 400 mg film-coated tablets 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 section5.2).

*Hepatic impairment*
No dose adjustment of Sofosbuvir 400 mg film-coated tablets 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 400 mg film-coated tablets have not been established in patients with decompensated cirrhosis.

*Patients awaiting liver transplantation*
The duration of administration of Sofosbuvir 400 mg film-coated tablets 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).

*Paediatric population*
The safety and efficacy of Sofosbuvir 400 mg film-coated tablets in children and adolescents aged <18 years have not yet been established. No data 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 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.

## 4.2 Contraindications

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

## 4.3 Special warnings and precautions for use

General
Sofosbuvir 400 mg film-coated tablets 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 400 mg film-coated tablets are permanently discontinued, Sofosbuvir 400 mg film-coated tablets should also be discontinued (see section 4.2). Consult the Summary of Product Characteristics for co-prescribed medicinal products before starting therapy with Sofosbuvir 400 mg film-coated tablets.

Treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection
Sofosbuvir 400 mg film-coated tablets has not been studied in a Phase 3 study in treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection. Thus, the optimal treatment duration in this population has not been established (see 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 400 mg film-coated tablets in patients with genotype5 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 and 6 HCV infection with Sofosbuvir 400 mg film-coated tablets 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
Sofosbuvir 400 mg film-coated tablets should only be co-administered with other direct-acting antiviral medicinal products if the benefit is considered to outweigh the risks based upon available data. There are no data to support the co-administration of Sofosbuvir 400 mg film-coated tablets and telaprevir or boceprevir. Such co-administration is not recommended (see also section 4.5).

Pregnancy and concomitant use with ribavirin
When Sofosbuvir 400 mg film-coated tablets 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 potent P-gp inducers

Medicinal products that are potent P-glycoprotein (P-gp) inducers in the intestine (e.g. rifampicin, St. John's wort *[Hypericum perforatum]*, carbamazepine and phenytoin) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir 400 mg film- coated tablets. Such medicinal products should not be used with Sofosbuvir 400 mg film-coated tablets (see section 4.5).

Renal impairment

The safety of Sofosbuvir 400 mg film-coated tablets 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 400 mg film-coated tablets 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

There are no data on the use of Sofosbuvir 400 mg film-coated tablets in patients with HCV/HBV co-infection.

Paediatric population

Sofosbuvir 400 mg film-coated tablets is not recommended for use in children and adolescents under 18 years of age because the safety and efficacy have not been established in this population.

**4.4 Interaction with other medicinal products and other forms of interaction**

Sofosbuvir is a nucleotide prodrug. After oral administration of Sofosbuvir 400 mg film-coated tablets,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 (e.g. rifampicin, St. John's wort, carbamazepine and phenytoin) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of Sofosbuvir 400 mg film-coated tablets and thus should not be used with Sofosbuvir 400 mg film-coated tablets (see section 4.4). Co-administration

of Sofosbuvir 400 mg film-coated tablets with medicinal products that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration, thus Sofosbuvir 400 mg film-coated tablets 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 thatare substrates of these transporters.

The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity andhigh capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant medicinal products (see section 5.2).

Other interactions

Drug interaction information for Sofosbuvir 400 mg film-coated tablets 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 400 mg film-coated tablets and other medicinal products**

| **Medicinal product by therapeutic areas** | **Effects on drug levels. Mean ratio (90% confidence interval) for AUC, Cmax, Cmina,b** | **Recommendation concerning co-administration with Sofosbuvir 400 mg film-coated tablets** |
|---|---|---|
| ***ANALEPTICS*** | | |
| Modafinil | Interaction not studied.<br>*Expected:*<br>↓ Sofosbuvir<br>↓ GS-331007 | Co-administration of Sofosbuvir 400 mg film-coated tablets with modafinil is expected to decrease the concentration of Sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir 400 mg film-coated tablets. Such co-administration is not recommended. |

| **Medicinalproduct by therapeutic areas** | **Effects on drug levels. Mean ratio (90% confidence interval) for AUC, Cmax, Cmina,b** | **Recommendation concerning co-administration with Sofosbuvir 400 mg film-coated tablets** |
|---|---|---|
| ***ANTICONVULSANTS*** | | |
| Carbamazepine<br>Phenytoin | Interactio notstudie n d.<br>*Expected:* | Co-administration of Sofosbuvir 400 mg film-coated tablets with carbamazepine, phenytoin, |

| | | |
|---|---|---|
| Phenobarbital<br>Oxcarbazepine | ↓ Sofosbuvir<br>↓ GS-331007 | phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir 400 mg film-coated tablets. Such co-administration is not recommended.<br>Sofosbuvir 400 mg film-coated tablets should not be used with carbamazepine, phenytoin, phenobarbital or oxcarbazepine, potent intestinal P-gp inducers (see section 4.4). |
| ***ANTIMYCOBACTERIALS*** | | |
| Rifabutin<br>Rifampicin<br>Rifapentine | Interaction not studied.<br>*Expected:*<br>↓ Sofosbuvir<br>↓ GS-331007 | Co-administration of Sofosbuvir 400 mg film-coated tablets with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of Sofosbuvir 400 mg film-coated tablets. Such co-administration is not recommended.<br>Sofosbuvir 400 mg film-coated tablets should not be used with rifampicin, a potent intestinal P-gp inducer (see section 4.4). |
| ***HERBAL SUPPLEMENTS*** | | |
| St. John's wort *(Hypericum perforatum)* | Interaction not studied.<br>*Expected:*<br>↓ Sofosbuvir<br>↓ GS-331007 | Sofosbuvir 400 mg film-coated tablets should not be used with St. John's wort, a potent intestinal P-gp inducer (see section 4.4). |
| ***HCV ANITIVIRAL AGENTS: HCV PROTEASE INHIBITORS*** | | |
| Boceprevir (BOC)<br>Telaprevir (TPV) | Interaction not studied.<br>*Expected:*<br>↑ Sofosbuvir (TPV)<br>↔ Sofosbuvir (BOC)<br>↔ GS-331007 (TPV or BOC) | No drug-drug interactio data exists regarding the co- administration of Sofosbuvir 400 mg film-coated tablets with boceprevir or telaprevir. |
| ***NARCOTIC ANALGESICS*** | | |

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|---|---|---|
| Methadone[f] (Methadone maintenance therapy [30 to 130 mg/daily]) | *R-methadone*<br>↔ Cmax 0.99 (0.85, 1.16)<br>↔ AUC 1.01 (0.85, 1.21)<br>↔ Cmin 0.94 (0.77, 1.14)<br><br>*S-methadone*<br>↔ Cmax 0.95 (0.79, 1.13)<br>↔ AUC 0.95 (0.77, 1.17)<br>↔ Cmin 0.95 (0.74, 1.22)<br><br>*Sofosbuvir*<br>↓ Cmax 0.95[c] (0.68, 1.33)<br>↑ AUC 1.30[c] (1.00, 1.69)<br>Cmin (NA)<br><br>*GS-331007*<br>↓ Cmax 0.73[c] (0.65, 0.83)<br>↔ AUC 1.04[c] (0.89, 1.22)<br>Cmin (NA) | No dose adjustment of sofosbuvir or methadone is required when sofosbuvir and methadone are used concomitantly. |

| **Medicinal product by therapeutic areas** | **Effects on drug levels. Mean ratio (90% confidence interval) for AUC, Cmax, Cmina,b** | **Recommendation concerning co-administration with Sofosbuvir 400 mg film-coated tablets** |
|---|---|---|
| ***IMMUNOSUPPRESSANTS*** | | |
| Ciclosporin[e] (600 mg single dose) | *Ciclosporin*<br>↔ Cmax 1.06 (0.94, 1.18)<br>↔ AUC 0.98 (0.85, 1.14)<br>Cmin (NA)<br><br>*Sofosbuvir*<br>↑ Cmax 2.54 (1.87, 3.45)<br>↑ AUC 4.53 (3.26, 6.30)<br>Cmin (NA) | No dose adjustment of sofosbuvir or ciclosporin is required when sofosbuvir and ciclosporin are used concomitantly. |

| | | |
|---|---|---|
| | *GS-331007*<br>↓ Cmax 0.60 (0.53, 0.69)<br>↔ AUC 1.04 (0.90, 1.20)<br>Cmin (NA) | |
| Tacrolimus[e]<br>(5 mg single dose) | *Tacrolimus*<br>↓ Cmax 0.73 (0.59, 0.90)<br>↔ AUC 1.09 (0.84, 1.40)<br>Cmin (NA)<br><br>*Sofosbuvir*<br>↓ Cmax 0.97 (0.65, 1.43)<br>↑ AUC 1.13 (0.81, 1.57)<br>Cmin (NA)<br><br>*GS-331007*<br>↔ Cmax 0.97 (0.83, 1.14)<br>↔ AUC 1.00 (0.87, 1.13)<br>Cmin (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]<br>(600 mg once daily)[d] | *Efavirenz*<br>↔ Cmax 0.95 (0.85, 1.06)<br>↔ AUC 0.96 (0.91, 1.03)<br>↔ Cmin 0.96 (0.93, 0.98)<br><br>*Sofosbuvir*<br>↓ Cmax 0.81 (0.60, 1.10)<br>↔ AUC 0.94 (0.76, 1.16)<br>Cmin (NA)<br><br>*GS-331007*<br>↓ Cmax 0.77 (0.70, 0.84)<br>↔ AUC 0.84 (0.76, 0.92)<br>Cmin (NA) | No dose adjustment of sofosbuvir or efavirenz is required when sofosbuvir and efavirenz are used concomitantly. |

| | | |
|---|---|---|
| Emtricitabine[f]<br>(200 mg once daily)[d] | *Emtricitabine*<br>↔ Cmax 0.97 (0.88, 1.07)<br>↔ AUC 0.99 (0.94, 1.05)<br>↔ Cmin 1.04 (0.98, 1.11)<br>*Sofosbuvir*<br>↓ Cmax 0.81 (0.60, 1.10)<br>↔ AUC 0.94 (0.76, 1.16)<br>Cmin (NA)<br>*GS-331007*<br>↓ Cmax 0.77 (0.70, 0.84)<br>↔ AUC 0.84 (0.76, 0.92)<br>Cmin (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, Cmax, Cmina,b** | **Recommendation concerning co-administration with Sofosbuvir 400 mg film-coated tablets** |
|---|---|---|
| Tenofovir disoproxil fumarate[f]<br>(300 mg once daily)[d] | *Tenofovir*<br>↑ Cmax 1.25 (1.08, 1.45)<br>↔ AUC 0.98 (0.91, 1.05)<br>↔ Cmin 0.99 (0.91, 1.07)<br>*Sofosbuvir*<br>↓ Cmax 0.81 (0.60, 1.10)<br>↔ AUC 0.94 (0.76, 1.16)<br>Cmin (NA)<br>*GS-331007*<br>↓ Cmax 0.77 (0.70, 0.84)<br>↔ AUC 0.84 (0.76, 0.92)<br>Cmin (NA) | No dose adjustment of sofosbuvir or tenofovir disoproxil fumarate is required when sofosbuvir and tenofovir disoproxil fumarate are used concomitantly. |

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|---|---|---|
| Rilpivirine[f]<br>(25 mg once daily) | *Rilpivirine*<br>↔ Cmax 1.05 (0.97, 1.15)<br>↔ AUC 1.06 (1.02, 1.09)<br>↔ Cmin 0.99 (0.94, 1.04)<br>*Sofosbuvir*<br>↑ Cmax 1.21 (0.90, 1.62)<br>↔ AUC 1.09 (0.94, 1.27)<br>Cmin (NA)<br>*GS-331007*<br>↔ Cmax 1.06 (0.99, 1.14)<br>↔ AUC 1.01 (0.97, 1.04)<br>Cmin (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]<br>(800/100 mg once daily) | *Darunavir*<br>↔ Cmax 0.97 (0.94, 1.01)<br>↔ AUC 0.97 (0.94, 1.00)<br>↔ Cmin 0.86 (0.78, 0.96)<br>*Sofosbuvir*<br>↑ Cmax 1.45 (1.10, 1.92)<br>↑ AUC 1.34 (1.12, 1.59)<br>Cmin (NA)<br>*GS-331007*<br>↔ Cmax 0.97 (0.90, 1.05)<br>↔ AUC 1.24 (1.18, 1.30)<br>Cmin (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]<br>(400 mg twice daily) | *Raltegravir*<br>↓ Cmax 0.57 (0.44, 0.75)<br>↓ AUC 0.73 (0.59, 0.91)<br>↔ Cmin 0.95 (0.81, 1.12) | No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly. |

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|---|---|---|
| | *Sofosbuvir*<br>↔ Cmax 0.87 (0.71, 1.08)<br>↔ AUC 0.95 (0.82, 1.09)<br>Cmin (NA)<br><br>*GS-331007*<br>↔ Cmax 1.09 (0.99, 1.20)<br>↔ AUC 1.03 (0.97, 1.08)<br>Cmin (NA) | |
| **Medicinal product by therapeutic areas** | **Effects on drug levels. Mean ratio (90% confidence interval) for AUC, Cmax, Cmina,b** | **Recommendation concerning co-administration with Sofosbuvir 400 mg film-coated tablets** |
| ***ORAL CONTRACEPTIVES*** | | |

| | | |
|---|---|---|
| Norgestimate/ ethinyl estradiol | *Norgestromin*<br>↔ Cmax 1.06 (0.93, 1.22)<br>↔ AUC 1.05 (0.92, 1.20)<br>Cmin (NA)<br><br>*Norgestrel*<br>↔ Cmax 1.18 (0.99, 1.41)<br>↔ AUC 1.19 (0.98, 1.44)<br>Cmin (NA)<br><br>*Ethinyl estradiol*<br>↔ Cmax 1.14 (0.96, 1.36)<br>↔ AUC 1.08 (0.93, 1.25)<br>Cmin (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 Atripla

e. Bioequivalence boundary 80%-125%

f. Equivalence boundary 70%-143%

Medicinal products that are potent P-gp inducers in the intestine (rifampicin, St. John's wort, carbamazepine and phenytoin) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect. For this reason, sofosbuvir should not be co-administered with known inducers of P-gp.

## 4.5 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

When Sofosbuvir 400 mg film-coated tablets 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 as recommended in the Summary of Product Characteristics for ribavirin. 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 sofosbuvirin 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 ratrelative 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 400 mg film-coated tabletsduring 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 seesection 5.3).

A risk to newborns/infants cannot be excluded. Therefore, Sofosbuvir 400 mg film-coated tablets should not be used during breast-feeding.

Fertility
No human data on the effect of Sofosbuvir 400 mg film-coated tablets on fertility are available. Animal studies do not indicate harmful effects on fertility.

## 4.6 Effects on ability to drive and use machines

Sofosbuvir 400 mg film-coated tablets has moderate influence on the 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).

## 4.7 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 expectedadverse 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 400 mg film-coated tablets 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 (seesection 5.1).

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.8 Overdose

The highest documented dose of sofosbuvir was a single supra therapeutic dose of sofosbuvir 1,200 mgadministered 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 400 mg film-coated tablets. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir 400 mg film-coated tablets 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 (the active metabolite of sofosbuvir) is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity

In HCV replicon assays, the effective concentration ($EC_{50}$) values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a were 0.04, 0.11, 0.05, 0.05 and 0.04 μM, respectively, and $EC_{50}$ values of sofosbuvir against chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a were 0.014 to 0.015 μM. The mean ± SD $EC_{50}$ of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.068 ± 0.024 μM for genotype 1a (n = 67), 0.11 ± 0.029 μM for genotype 1b (n = 29), 0.035 ± 0.018 μM for genotype 2 (n = 15) and 0.085 ± 0.034 μM for genotype 3a (n = 106). In these assays, the *in vitro* antiviral activity of sofosbuvir against the less common genotypes 4, 5 and 6 was similar to that observed for genotypes 1, 2 and 3.

The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

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 991 subjects who received sofosbuvir in Phase 3 studies, 226 subjects qualified for resistance analysis due to virologic failure or early study drug discontinuation and having

HCV RNA >1,000 IU/mL. Post-baseline NS5B sequences were available for 225 of the 226 subjects, with deep sequencing data (assay cutoff of 1%) from 221 of these subjects. The sofosbuvir-associated resistance substitution S282T was not detected in any of these subjects by deep sequencing or population sequencing. The S282T substitution in NS5B was detected in a single subject receiving Sofosbuvir 400 mg film-coated tablets 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.

<u>Effect of baseline HCV polymorphisms on treatment outcome</u>

Baseline NS5B sequences were obtained for 1,292 subjects from Phase 3 studies by population sequencing and the S282T substitution was not detected in any subject with available baseline sequence. In an analysis evaluating the effect of baseline polymorphisms on treatment outcome, no statistically significant association was observed between the presence of any HCV NS5B variant at baseline and treatment outcome.

<u>Cross-resistance</u>

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 and was not guided by subjects' HCV RNA levels (no response guided algorithm).

Plasma HCV RNA values were measured during the clinical studies using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU/mL. 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 LLOQ at 12 weeks after the end of treatment (SVR12).

*Clinical studies in subjects with genotype 1, 4, 5 and 6 chronic hepatitis C Treatment-naïve subjects - NEUTRINO (study 110)*

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

Treated subjects (n = 327) had a median age of 54 years (range: 19 to 70); 64% of the subjects were male; 79% were White; 17% were Black; 14% were Hispanic or Latino; mean body mass index was 29 kg/m$^2$ (range: 18 to 56 kg/m$^2$); 78% had baseline HCV RNA greater than 6 log10 IU/mL; 17% had cirrhosis; 89% had HCV genotype 1 and 11% had HCV genotype 4, 5 or 6. Table 5 presents the response rates for the treatment group of sofosbuvir + peginterferon alfa + ribavirin.

**Table 5: Response rates in study NEUTRINO**

| | **SOF+PEG+RBV 12 weeks (n = 327)** |
|---|---|
| Overall SVR12 | 91% (296/327) |
| Outcome for subjects without SVR12 | |
| On-treatment virologic | 0/327 |

| | |
|---|---|
| failure | |
| Relapse[a] | 9% (28/326) |
| Other[b] | 1% (3/327) |

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).

Response rates for selected subgroups are presented in Table 6.

**Table 6: SVR12 rates for selected subgroups in NEUTRINO**

| | **SOF+PEG+RBV 12 weeks (n = 327)** |
|---|---|
| Genotype | |
| Genotype 1 | 90% (262/292) |
| Genotype 4, 5 or 6 | 97% (34/35) |
| Cirrhosis | |
| No | 93% (253/273) |
| Yes | 80% (43/54) |
| Race | |
| Black | 87% (47/54) |
| Non-Black | 91% (249/273) |

SVR12 rates were similarly high in subjects with baseline IL28B C/C allele [94/95 (99%)] and non-C/C (C/T or T/T) allele [202/232 (87%)].

27/28 patients with genotype 4 HCV achieved SVR12. A single subject with genotype 5 and all 6 subjects with genotype 6 HCV infection in this study achieved SVR12.

*Clinical studies in subjects with genotype 2 and 3 chronic hepatitis C*

*Treatment-naïve adults - FISSION (study 1231)*

FISSION was a randomised, open-label, active-controlled study that evaluated 12 weeks of treatment with sofosbuvir and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 2 or 3 HCV infection. The ribavirin doses used in the sofosbuvir + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1,000-1,200 mg/day and 800 mg/day regardless of weight, respectively. Subjects were randomised in a 1:1 ratio and stratified by cirrhosis (presence *versus* absence), HCV genotype (2 *versus* 3) and baseline HCV RNA level (<6 log10 IU/mL *versus* ≥6 log10 IU/mL). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio.

Treated subjects (n = 499) had a median age of 50 years (range: 19 to 77); 66% of the subjects were male; 87% were White; 3% were Black; 14% were Hispanic or Latino; mean body mass index was 28 kg/m$^2$ (range: 17 to 52 kg/m$^2$); 57% had

baseline HCV RNA levels greater than 6 log10 IU/mL; 20% had cirrhosis; 72% had HCV genotype 3. Table 7 presents the response rates for the treatment groups of sofosbuvir + ribavirin and peginterferon alfa + ribavirin.

**Table 7: Response rates in study FISSION**

| | **SOF+RBV 12 weeks (n = 256)[a]** | **PEG+RBV 24 weeks (n = 243)** |
|---|---|---|
| Overall SVR12 | 67% (171/256) | 67% (162/243) |
| Genotype 2 | 95% (69/73) | 78% (52/67) |
| Genotype 3 | 56% (102/183) | 63% (110/176) |
| Outcome for subjects withoutSVR12 | | |
| On-treatment virologic failure | < 1% (1/256) | 7% (18/243) |
| Relapse[b] | 30% (76/252) | 21% (46/217) |
| Other[c] | 3% (8/256) | 7% (17/243) |

a. The efficacy analysis includes 3 subjects with recombinant genotype 2/1 HCV infection.
b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

The difference in the overall SVR12 rates between sofosbuvir + ribavirin and peginterferon alfa + ribavirin treatment groups was 0.3% (95% confidence interval: -7.5% to 8.0%) and the study met thepredefined non-inferiority criterion.

Response rates for subjects with cirrhosis at baseline are presented in Table 8 by HCV genotype.

**Table 8: SVR12 rates by cirrhosis and genotype in study FISSION**

| | **Genotype 2** | | **Genotype 3** | |
|---|---|---|---|---|
| | **SOF+RBV 12 weeks (n = 73)[a]** | **PEG+RBV 24 weeks (n = 67)** | **SOF+RBV 12 weeks (n = 183)** | **PEG+RBV 24 weeks (n = 176)** |
| Cirrhosis | | | | |
| No | 97% (59/61) | 81% (44/54) | 61% (89/145) | 71% (99/139) |
| Yes | 83% (10/12) | 62% (8/13) | 34% (13/38) | 30% (11/37) |

a. The efficacy analysis includes 3 subjects with recombinant genotype 2/1 HCV infection.

*Interferon intolerant, ineligible or unwilling adults - POSITRON (study 107)*
POSITRON was a randomised, double-blinded, placebo-controlled study that evaluated 12 weeks of treatment with sofosbuvir and ribavirin (n = 207) compared

to placebo (n = 71) in subjects who are interferon intolerant, ineligible or unwilling. Subjects were randomised in 3:1 ratio and stratified by cirrhosis (presence *versus* absence).

Treated subjects (n = 278) had a median age of 54 years (range: 21 to 75); 54% of the subjects were male; 91% were White; 5% were Black; 11% were Hispanic or Latino; mean body mass index was 28 $kg/m^2$ (range: 18 to 53 $kg/m^2$); 70% had baseline HCV RNA levels greater than 6 log10 IU/mL; 16% had cirrhosis; 49% had HCV genotype 3. The proportions of subjects who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most subjects had no prior HCV treatment (81.3%). Table 9 presents the response rates for the treatment groups of sofosbuvir + ribavirin and placebo.

**Table 9: Response rates in study POSITRON**

| | **SOF+RBV 12 weeks (n = 207)** | **Placebo 12 weeks (n = 71)** |
|---|---|---|
| Overall SVR12 | 78% (161/207) | 0/71 |
| Genotype 2 | 93% (101/109) | 0/34 |
| Genotype 3 | 61% (60/98) | 0/37 |
| Outcome for subjects withoutSVR12 | | |
| On-treatment virologic failure | 0/207 | 97% (69/71) |
| Relapse[a] | 20% (42/205) | 0/0 |
| Other[b] | 2% (4/207) | 3% (2/71) |

a. The denominator for relapse is the number of 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).

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

Table 10 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

**Table 10: SVR12 rates for selected subgroups by genotype in POSITRON**

| | **SOF+RBV 12 weeks** | |
|---|---|---|
| | **Genotype 2 (n = 109)** | **Genotype 3 (n = 98)** |
| Cirrhosis | | |

| | | |
|---|---|---|
| No | 92% (85/92) | 68% (57/84) |
| Yes | 94% (16/17) | 21% (3/14) |
| Interferon classification | | |
| Ineligible | 88% (36/41) | 70% (33/47) |
| Intolerant | 100% (9/9) | 50% (4/8) |
| Unwilling | 95% (56/59) | 53% (23/43) |

*Previously treated adults - FUSION (study 108)*

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

Treated subjects (n = 201) had a median age of 56 years (range: 24 to 70); 70% of the subjects were male; 87% were White; 3% were Black; 9% were Hispanic or Latino; mean body mass index was 29 kg/m$^2$ (range: 19 to 44 kg/m$^2$); 73% had baseline HCV RNA levels greater than 6 log10 IU/mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. Table 11 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 16 weeks.

**Table 11: Response rates in study FUSION**

| | **SOF+RBV 12 weeks (n = 103)[a]** | **SOF+RBV 16 weeks (n = 98)[a]** |
|---|---|---|
| Overall SVR12 | 50% (51/103) | 71% (70/98) |
| Genotype 2 | 82% (32/39) | 89% (31/35) |
| Genotype 3 | 30% (19/64) | 62% (39/63) |
| Outcome for subjects without SVR12 | | |
| On-treatment virologic failure | 0/103 | 0/98 |
| Relapse[b] | 48% (49/103) | 29% (28/98) |
| Other[c] | 3% (3/103) | 0/98 |

a. The efficacy analysis includes 6 subjects with recombinant genotype 2/1 HCV infection.
b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 12 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

**Table 12: SVR12 rates for selected subgroups by genotype in study FUSION**

| | Genotype 2 | | Genotype 3 | |
|---|---|---|---|---|
| | **SOF+RBV 12 weeks (n = 39)** | **SOF+RBV 16 weeks (n = 35)** | **SOF+RBV 12 weeks (n = 64)** | **SOF+RBV 16 weeks (n = 63)** |
| Cirrhosis | | | | |
| No | 90% (26/29) | 92% (24/26) | 37% (14/38) | 63% (25/40) |
| Yes | 60% (6/10) | 78% (7/9) | 19% (5/26) | 61% (14/23) |
| Response to prior HCV treatment | | | | |
| Relapser | 86% (25/29) | 89% (24/27) | 31% (15/49) | 65% (30/46) |
| Nonresponder | 70% (7/10) | 88% (7/8) | 27% (4/15) | 53% (9/17) |

*Treatment-naïve and previously treated adults - VALENCE (study 133)*

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

Treated subjects (n = 419) had a median age of 51 years (range: 19 to 74); 60% of the subjects were male; median body mass index was 25 kg/m$^2$ (range: 17 to 44 kg/m$^2$); the mean baseline HCV RNA level was 6.4 log10 IU/mL; 21% had cirrhosis; 78% had HCV genotype 3; 65% were prior relapsers. Table 13 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 24 weeks.

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

**Table 13: Response rates in study VALENCE**

| | **Genotype 2 SOF+RBV 12 weeks (n = 73)** | **Genotype 3 SOF+RBV 12 weeks (n = 11)** | **Genotype 3 SOF+RBV 24 weeks (n = 250)** |
|---|---|---|---|
| Overall SVR12 | 93% (68/73) | 27% (3/11) | 84% (210/250) |
| Outcome for subjects | | | |

| | | | |
|---|---|---|---|
| without SVR12 | | | |
| On-treatment virologic failure | 0% (0/73) | 0% (0/11) | 0.4% (1/250) |
| Relapse[a] | 7% (5/73) | 55% (6/11) | 14% (34/249) |
| Other[b] | 0% (0/73) | 18% (2/11) | 2% (5/250) |

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).

Table 14 presents the subgroup analysis by genotype for cirrhosis and exposure to prior HCV treatment.

**Table 14: SVR12 rates for selected subgroups by genotype in study VALENCE**

| | **Genotype 2 SOF+RBV 12 weeks (n = 73)** | **Genotype 3 SOF+RBV 24 weeks (n = 250)** |
|---|---|---|
| Treatment-naïve | 97% (31/32) | 93% (98/105) |
| Non-cirrhotic | 97% (29/30) | 93% (86/92) |
| Cirrhotic | 100% (2/2) | 92% (12/13) |
| Treatment-experienced | 90% (37/41) | 77% (112/145) |
| Non-cirrhotic | 91% (30/33) | 85% (85/100) |
| Cirrhotic | 88% (7/8) | 60% (27/45) |

*SVR12 to SVR24 concordance*

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

Clinical efficacy and safety in special populations

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

Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 12 or 24 weeks of treatment with sofosbuvir and ribavirin in subjects with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV-1. Genotype 2 and 3 subjects were either treatment-naïve or experienced, whereas genotype 1 subjects were naïve to prior treatment. Treatment duration was 12 weeks in treatment-naïve subjects with genotype 2 or 3 HCV infection, and 24 weeks in treatment-experienced subjects with genotype 3 HCV infection, as well as subjects with genotype 1 HCV infection. Subjects received 400 mg sofosbuvir and weight-based ribavirin (1,000 mg for subjects weighing <75 kg or 1,200 mg for subjects weighing ≥75 kg). Subjects were either not on antiretroviral therapy with a CD4+

cell count >500 cells/mm$^3$ or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm$^3$. 95% of patients received antiretroviral therapy at the time of enrolment. Preliminary SVR12 data are available for 210 subjects.

Table 15 presents the response rates by genotype and exposure to prior HCV treatment.

**Table 15: Response rates in study PHOTON-1**

| | **Genotype 2/3 treatment-naïve SOF+RBV 12 weeks (n = 68)** | **Genotype 2/3 treatment-experienced SOF+RBV 24 weeks (n = 28)** | **Genotype 1 treatment-naïve SOF+RBV 24 weeks (n = 114)** |
|---|---|---|---|
| Overall SVR12 | 75% (51/68) | 93% (26/28) | 76% (87/114) |
| Outcome for subjects without SVR12 | | | |
| On-treatment virologic failure | 1% (1/68) | 0/28 | 1% (1/114) |
| Relapse[a] | 18% (12/67) | 7% (2/28) | 22% (25/113) |
| Other[b] | 6% (4/68) | 0/28 | 1% (1/114) |

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).

Table 16 presents the subgroup analysis by genotype for cirrhosis.

**Table 16: SVR12 rates for selected subgroups by genotype in study PHOTON-1**

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

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

*Patients awaiting liver transplantation - Study 2025*

Sofosbuvir was studied in HCV infected subjects 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). HCV infected subjects, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the
MILAN criteria received 400 mg sofosbuvir and 1,000-1,200 mg ribavirin daily for a maximum of 24 weeks, subsequently amended to 48 weeks, or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 subjects who received sofosbuvir and ribavirin; the majority of subjects had HCV genotype 1, 44 subjects were CPT class A and 17 subjects were CPT class
B. Of these 61 subjects, 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 41 subjects transplanted with HCV RNA <LLOQ is described in Table
17. Duration of viral suppression prior to transplantation was the most predictive factor for pTVR in those who were HCV RNA <LLOQ at the time of transplantation.

**Table 17: Virologic response post-transplant in subjects with HCV RNA <LLOQ at the time of liver transplantation**

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

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

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

Overview of outcomes by therapeutic regimen and treatment duration, a comparison across studies The following tables (Table 18 to Table 21) present data from Phase 2 and Phase 3 studies relevant to the dosing to help clinicians determine the best regimen for individual patients.

**Table 18: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 1 HCV infection**

| **Patient population (Study number/name)** | **Regimen/Duration** | **Subgroup** | **SVR12 rate % (n/N)** |
|---|---|---|---|
| | | Overall | 90% (262/292) |

| | | | |
|---|---|---|---|
| Treatment-naïve[a] (NEUTRINO) | SOF+PEG+RBV 12 weeks | Genotype 1a | 92% (206/225) |
| | | Genotype 1b | 83% (55/66) |
| | | No cirrhosis | 93% (253/273) |
| | | Cirrhosis | 80% (43/54) |
| Treatment-naïve and co-infected with HIV (PHOTON-1) | SOF+RBV 24 weeks | Overall | 76% (87/114) |
| | | Genotype 1a | 82% (74/90) |
| | | Genotype 1b | 54% (13/24) |
| | | No cirrhosis | 77% (84/109) |
| | | Cirrhosis | 60% (3/5) |
| Treatment-naïve (QUANTUM[b] and 11-1-0258[b]) | SOF+RBV 24 weeks | Overall[c] | 65% (104/159) |
| | | Genotype 1a[c] | 69% (84/121) |
| | | Genotype 1b[c] | 53% (20/38) |
| | | No cirrhosis[c] | 68% (100/148) |
| | | Cirrhosis[c] | 36% (4/11) |

n = number of subjects with SVR12 response; N = total number of subjects per group.

a. For previously treated patients with genotype 1 HCV infection, no data exists with the combination of sofosbuvir, peginterferon alfa and ribavirin. 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 (prior null response to peginterferon alfa and ribavirin therapy, advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).

b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. c. Summary data from both studies.

**Table 19: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 2 HCV infection**

| **Patient population (Study number/name)** | **Regimen/Duration** | **Subgroup** | **SVR12 rate % (n/N)** |
|---|---|---|---|
| Treatment-naïve (FISSION) | SOF+RBV 12 weeks | Overall | 95% (69/73) |
| | | No cirrhosis | 97% (59/61) |
| | | Cirrhosis | 83% (10/12) |
| Interferon intolerant, ineligibleor unwilling (POSITRON) | SOF+RBV 12 weeks | Overall | 93% (101/109) |
| | | No cirrhosis | 92% (85/92) |
| | | Cirrhosis | 94% (16/17) |
| Treatment-experienced (FUSION) | SOF+RBV 12 weeks | Overall | 82% (32/39) |
| | | No cirrhosis | 90% (26/29) |
| | | Cirrhosis | 60% (6/10) |
| | | Overall | 97% (31/32) |

| | | | |
|---|---|---|---|
| Treatment-naïve (VALENCE) | SOF+RBV 12 weeks | No cirrhosis | 97% (29/30) |
| | | Cirrhosis | 100% (2/2) |
| Treatment-experienced (VALENCE) | SOF+RBV 12 weeks | Overall | 90% (37/41) |
| | | No cirrhosis | 91% (30/33) |
| | | Cirrhosis | 88% (7/8) |
| Treatment-experienced (FUSION) | SOF+RBV 16 weeks | Overall | 89% (31/35) |
| | | No cirrhosis | 92% (24/26) |
| | | Cirrhosis | 78% (7/9) |
| Treatment-naïve co-infected with HIV (PHOTON-1) | SOF+RBV 12 weeks | Overall | 88% (23/26) |
| | | No cirrhosis | 88% (22/25) |
| | | Cirrhosis | 100% (1/1) |
| Treatment-experienced co-infected with HIV (PHOTON-1) | SOF+RBV 24 weeks | Overall[a] | 93% (14/15) |
| | | No cirrhosis[a] | 92% (12/13) |
| | | Cirrhosis[a] | 100% (2/2) |
| Treatment-naïve (ELECTRON[b] and PROTON[b]) | SOF+PEG+RBV 12 weeks | Overall[c] | 96% (25/26) |
| Treatment-experienced (LONESTAR-2[b]) | SOF+PEG+RBV 12 weeks | Overall | 96% (22/23) |
| | | No cirrhosis | 100% (9/9) |
| | | Cirrhosis | 93% (13/14) |

n = number of subjects with SVR12 response; N = total number of subjects per group.

a. These data are preliminary.

b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. In the ELECTRON study (N = 11), the duration of peginterferon alfa ranged from 4-12 weeks in combination with sofosbuvir + ribavirin. c. All patients were non-cirrhotic in these two studies.

**Table 20: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 3 HCV infection**

| **Patient population (Study number/name)** | **Regimen/Duration** | **Subgroup** | **SVR12 rate % (n/N)** |
|---|---|---|---|
| Treatment-naïve (FISSION) | SOF+RBV 12 weeks | Overall | 56% (102/183) |
| | | No cirrhosis | 61% (89/145) |
| | | Cirrhosis | 34% (13/38) |
| Interferon intolerant, ineligible or unwilling (POSITRON) | SOF+RBV 12 weeks | Overall | 61% (60/98) |
| | | No cirrhosis | 68% (57/84) |
| | | Cirrhosis | 21% (3/14) |
| Treatment- | SOF+RBV 12 weeks | Overall | 30% (19/64) |
| | | No cirrhosis | 37% (14/38) |

| | | | |
|---|---|---|---|
| experienced (FUSION) | | Cirrhosis | 19% (5/26) |
| Treatment-experienced (FUSION) | SOF+RBV 16 weeks | Overall | 62% (39/63) |
| | | No cirrhosis | 63% (25/40) |
| | | Cirrhosis | 61% (14/23) |
| Treatment-naïve (VALENCE) | SOF+RBV 24 weeks | Overall | 93% (98/105) |
| | | No cirrhosis | 94% (86/92) |
| | | Cirrhosis | 92% (12/13) |
| Treatment-experienced (VALENCE) | SOF+RBV 24 weeks | Overall | 77% (112/145) |
| | | No cirrhosis | 85% (85/100) |
| | | Cirrhosis | 60% (27/45) |
| Treatment-naïve co-infected with HIV (PHOTON-1) | SOF+RBV 12 weeks | Overall | 67% (28/42) |
| | | No cirrhosis | 67% (24/36) |
| | | Cirrhosis | 67% (4/6) |
| Treatment-experienced co-infected with HIV (PHOTON-1) | SOF+RBV 24 weeks | Overall[a] | 92% (12/13) |
| | | No cirrhosis[a] | 100% (8/8) |
| | | Cirrhosis[a] | 80% (4/5) |
| Treatment-naïve (ELECTRON[b] and PROTON[b]) | SOF+PEG+RBV 12 weeks | Overall[c] | 97% (38/39) |
| Treatment-experienced (LONESTAR-2[b]) | SOF+PEG+RBV 12 weeks | Overall | 83% (20/24) |
| | | No cirrhosis | 83% (10/12) |
| | | Cirrhosis | 83% (10/12) |

n = number of subjects with SVR12 response; N = total number of subjects per group.

a. These data are preliminary.

b. These are exploratory or Phase 2 studies. The outcomes should be interpreted with caution, as subject numbers are small and SVR rates may be impacted by the selection of patients. In the ELECTRON study (N = 11), the duration of peginterferon alfa ranged from 4-12 weeks in combination with sofosbuvir + ribavirin. c. All patients were non-cirrhotic in these two studies.

**Table 21: Outcomes by therapeutic regimen and treatment duration, a comparison across studies in genotype 4, 5 and 6 HCV infection**

| **Patient population (Study number/name)** | **Regimen/Duration** | **Subgroup** | **SVR12 rate % (n/N)** |
|---|---|---|---|
| Treatment-naïve (NEUTRINO) | SOF+PEG+RBV 12 weeks | Overall | 97% (34/35) |
| | | No cirrhosis | 100% (33/33) |
| | | Cirrhosis | 50% (1/2) |

n = number of subjects with SVR12 response; N = total number of subjects per group.

*Paediatric population*
The European Medicines Agency has deferred the obligation to submit the results of studies with sofosbuvir in one or more subsets of the paediatric populations in the treatment of chronic hepatitis C (see section 4.2 for information on paediatric use).

## 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. Following oral administration, sofosbuvir was absorbed quickly and the peak plasma concentration was observed ~0.5- 2 hour post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose. Based on population pharmacokinetic analysis in 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.

*Effects of food*
Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised highfat 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 theformation 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 mgto 400 mg.

Pharmacokinetics in special populations

*Gender and race*

No clinically relevant pharmacokinetic differences due to gender or race have been identified forsofosbuvir 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 400 mg film-coated tablets was administered 1hour 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 400 mg film-coated tablets 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*

The pharmacokinetics of sofosbuvir and GS-331007 in paediatric subjects have not been established (see section 4.2).

<u>Pharmacokinetic/pharmacodynamic relationship(s)</u>

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 400mg 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 behavior, 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

Tablet core
Mannitol,
Microcrystalline cellulose,
Croscarmellose Sodium,
Colloidal Silicon Dioxide,
Magnesium Stearate,

Film-coating

Polyvinyl alcohol, Titanium dioxide, Macrogol, Talc, Iron Oxide Red, Iron Oxide yellow and Ferroso ferric oxide

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
24 Months.

**6.4 Special precautions for storage**
This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**
Sofosbuvir Tablets 400 mg are supplied in blue high-density polyethylene (HDPE) bottles containing 28film-coated tablets with a silica gel desiccant.

**6.6 Special precautions for disposal**
Any unused medicinal product or waste material should be disposed of in accordance with localrequirements.

**7 MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSESMarketing Authorization Holder:**

Mylan Laboratories Limited,
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**Manufacturing site Address:**
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Maharashtra, INDIA

**8 MARKETING AUTHORIZATION NUMBER**

TAN 21 HM 0096

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

29/03/2021

**10 DATE OF REVISION OF THE TEXT**

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