ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Harvoni 90 mg/400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 90 mg ledipasvir and 400 mg sofosbuvir.

Excipients with known effect:
Each film-coated tablet contains 156.8 mg of lactose (as monohydrate) and 261 micrograms of sunset yellow FCF aluminium lake.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange, diamond-shaped, film-coated tablet of dimensions 19 mm x 10 mm, debossed with “GSI” on one side and “7985” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Harvoni is indicated 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

Harvoni treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology
The recommended dose of Harvoni is one tablet once daily with or without food (see section 5.2).

Table 1: Recommended treatment duration for Harvoni and the recommended use of co-administered ribavirin for certain subgroups

Patient population*	**Treatment and duration**
Patients with genotype 1, 4, 5 or 6 CHC	
Patients without cirrhosis	Harvoni for 12 weeks. - Harvoni for 8 weeks may be considered in previously untreated genotype 1-infected patients (see section 5.1, ION-3 study). - Harvoni + ribavirin for 12 weeks or Harvoni (without ribavirin) for 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options (see section 4.4).
Patients with compensated cirrhosis	Harvoni + ribavirin for 12 weeks or Harvoni (without ribavirin) for 24 weeks. - Harvoni (without ribavirin) for 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options (see section 4.4).
Patients who are post-liver transplant without cirrhosis or with compensated cirrhosis	Harvoni + ribavirin for 12 weeks (see section 5.1). - Harvoni (without ribavirin) for 12 weeks (in patients without cirrhosis) or 24 weeks (in patients with cirrhosis) may be considered for patients who are ineligible for or intolerant to ribavirin.
Patients with decompensated cirrhosis, irrespective of transplant status	Harvoni + ribavirin for 12 weeks (see section 5.1). - Harvoni (without ribavirin) for 24 weeks may be considered in patients who are ineligible for or intolerant to ribavirin.
Patients with genotype 3 CHC	
Patients with compensated cirrhosis and/or prior treatment failure	Harvoni + ribavirin for 24 weeks (see sections 4.4 and 5.1).

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

When used in combination with ribavirin, refer also to the Summary of Product Characteristics of ribavirin.

In patients without decompensated cirrhosis requiring the addition of ribavirin to their treatment regimen (see Table 1), the daily dose of ribavirin is weight based (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg) and administered orally in two divided doses with food.

In patients with decompensated cirrhosis, ribavirin should be administered at a starting dose of 600 mg given in a divided daily dose. If the starting dose is well-tolerated, the dose can be titrated up to a maximum of 1,000-1,200 mg daily (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg). If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels.

Dose modification of ribavirin in patients taking 1,000-1,200 mg daily
If Harvoni is used in combination with ribavirin and 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 Harvoni

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

Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the originally assigned dose (1,000 mg to 1,200 mg daily).

Patients should be instructed that if vomiting occurs within 5 hours of dosing an additional tablet should be taken. If vomiting occurs more than 5 hours after dosing, no further dose is needed (see section 5.1).

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.

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

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

Hepatic impairment
No dose adjustment of Harvoni is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C) (see section 5.2). Safety and efficacy of ledipasvir/sofosbuvir have been established in patients with decompensated cirrhosis (see section 5.1).

Paediatric population
The safety and efficacy of Harvoni in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration
For oral use.

Patients should be instructed to swallow the tablet whole with or without food. Due to the bitter taste, it is recommended that the film-coated tablet is not chewed or crushed (see section 5.2).

4.3 Contraindications

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

Co-administration with rosuvastatin (see section 4.5).

Use with potent P-gp inducers
Medicinal products that are potent P-glycoprotein (P-gp) inducers in the intestine (rifampicin, rifabutin, St. John's wort *[Hypericum perforatum]*, carbamazepine, phenobarbital and phenytoin). Co-administration will significantly decrease ledipasvir and sofosbuvir plasma concentrations and could result in loss of efficacy of Harvoni (see section 4.5).

4.4 Special warnings and precautions for use

Harvoni should not be administered concomitantly with other medicinal products containing sofosbuvir.

Genotype-specific activity
Concerning recommended regimens with different HCV genotypes, see section 4.2. Concerning genotype-specific virological and clinical activity, see section 5.1.

The clinical data to support the use of Harvoni in patients infected with HCV genotype 3 are limited (see section 5.1). The relative efficacy of a 12-week regimen consisting of ledipasvir/sofosbuvir + ribavirin, compared to a 24-week regimen of sofosbuvir + ribavirin has not been investigated. A conservative 24 weeks of therapy is advised in all treatment-experienced genotype 3 patients and those treatment-naïve genotype 3 patients with cirrhosis (see section 4.2).

The clinical data to support the use of Harvoni in patients infected with HCV genotype 2 and 6 are limited (see section 5.1).

Severe bradycardia and heart block
Cases of severe bradycardia and heart block have been observed when Harvoni is used with concomitant amiodarone with or without other drugs that lower heart rate. The mechanism is not established.

The concomitant use of amiodarone was limited through the clinical development of sofosbuvir plus direct-acting antivirals (DAAs). Cases are potentially life threatening, therefore amiodarone should only be used in patients on Harvoni when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated.

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

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

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

Treatment of patients with prior exposure to HCV direct-acting antivirals
In patients who fail treatment with ledipasvir/sofosbuvir, selection of NS5A resistance mutations that substantially reduce the susceptibility to ledipasvir is seen in the majority of cases (see section 5.1). Limited data indicate that such NS5A mutations do not revert on long-term follow-up. There are presently no data to support the effectiveness of retreatment of patients who have failed ledipasvir/sofosbuvir with a subsequent regimen that contains an NS5A inhibitor. Similarly, there are presently no data to support the effectiveness of NS3/4A protease inhibitors in patients who previously failed prior therapy that included an NS3/4A protease inhibitor. Such patients may therefore be dependent on other drug classes for clearance of HCV infection. Consequently, consideration should be given to longer treatment for patients with uncertain subsequent retreatment options.

Renal impairment
No dose adjustment of Harvoni is required for patients with mild or moderate renal impairment. The safety of Harvoni has not been assessed 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. When Harvoni is used in combination with ribavirin refer also to the Summary of

Product Characteristics for ribavirin for patients with creatinine clearance (CrCl) < 50 mL/min (see section 5.2).

Patients with decompensated cirrhosis and/or who are awaiting liver transplant or post-liver transplant
The efficacy of ledipasvir/sofosbuvir in genotype 5 and genotype 6 HCV-infected patients with decompensated cirrhosis and/or who are awaiting liver transplant or post-liver transplant has not been investigated. Treatment with Harvoni should be guided by an assessment of the potential benefits and risks for the individual patient.

Use with moderate P-gp inducers
Medicinal products that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of Harvoni. Co-administration of such medicinal products is not recommended with Harvoni (see section 4.5).

Use with certain HIV antiretroviral regimens
Harvoni has been shown to increase tenofovir exposure, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Harvoni with the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving Harvoni concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Refer to tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate, or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate Summary of Product Characteristics for recommendations on renal monitoring.

Use with HMG-CoA reductase inhibitors
Co-administration of Harvoni and HMG-CoA reductase inhibitors (statins) can significantly increase the concentration of the statin, which increases the risk of myopathy and rhabdomyolysis (see section 4.5).

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

Paediatric population
Harvoni 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.

Excipients
Harvoni contains the azo colouring agent sunset yellow FCF aluminium lake (E110), which may cause allergic reactions. It also contains lactose. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

As Harvoni contains ledipasvir and sofosbuvir, any interactions that have been identified with these active substances individually may occur with Harvoni.

Potential for Harvoni to affect other medicinal products

Ledipasvir is an *in vitro* inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of co-administered substrates for these transporters. *In vitro* data indicate that ledipasvir may be a weak inducer of metabolising enzymes such as CYP3A4, CYP2C and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with ledipasvir/sofosbuvir. *In vitro* ledipasvir inhibits intestinal CYP3A4 and UGT1A1. Medicinal products that have a narrow therapeutic range and which are metabolised by these isoenzymes should be used with caution and carefully monitored.

Potential for other medicinal products to affect Harvoni

Ledipasvir and sofosbuvir are substrates of drug transporter P-gp and BCRP while GS-331007 is not.

Medicinal products that are potent P-gp inducers (rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may significantly decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of ledipasvir/sofosbuvir and thus are contraindicated with Harvoni (see section 4.3). Medicinal products that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of Harvoni. Co-administration with such medicinal products is not recommended with Harvoni (see section 4.4). Co-administration with medicinal products that inhibit P-gp and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS-331007 plasma concentration; Harvoni may be co-administered with P-gp and/or BCRP inhibitors. Clinically significant medicinal product interactions with ledipasvir/sofosbuvir mediated by CYP450s or UGT1A1 enzymes are not expected.

Patients treated with vitamin K antagonists

As liver function may change during treatment with Harvoni, a close monitoring of International Normalised Ratio (INR) values is recommended.

Interactions between Harvoni and other medicinal products

Table 3 provides a listing of established or potentially clinically significant medicinal product interactions (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 medicinal product interactions described are based on studies conducted with either ledipasvir/sofosbuvir or ledipasvir and sofosbuvir as individual agents, or are predicted medicinal product interactions that may occur with ledipasvir/sofosbuvir. The table is not all-inclusive.

Table 3: Interactions between Harvoni and other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
ACID REDUCING AGENTS		
		Ledipasvir solubility decreases as pH increases. Medicinal products that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids		
e.g. Aluminium or magnesium hydroxide; calcium carbonate	Interaction not studied. *Expected:* ↓ Ledipasvir ↔ Sofosbuvir ↔ GS-331007 (Increase in gastric pH)	It is recommended to separate antacid and Harvoni administration by 4 hours.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
H_2-receptor antagonists		
Famotidine (40 mg single dose)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c, d] Famotidine dosed simultaneously with Harvoni[d] Cimetidine[e] Nizatidine[e] Ranitidine[e]	Ledipasvir ↓ C_{max} 0.80 (0.69, 0.93) ↔ AUC 0.89 (0.76, 1.06) Sofosbuvir ↑ C_{max} 1.15 (0.88, 1.50) ↔ AUC 1.11 (1.00, 1.24) GS-331007 ↔ C_{max} 1.06 (0.97, 1.14) ↔ AUC 1.06 (1.02, 1.11) (Increase in gastric pH)	H_2-receptor antagonists may be administered simultaneously with or staggered from Harvoni at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Famotidine (40 mg single dose)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c, d] Famotidine dosed 12 hours prior to Harvoni[d]	Ledipasvir ↓ C_{max} 0.83 (0.69, 1.00) ↔ AUC 0.98 (0.80, 1.20) Sofosbuvir ↔ C_{max} 1.00 (0.76, 1.32) ↔ AUC 0.95 (0.82, 1.10) GS-331007 ↔ C_{max} 1.13 (1.07, 1.20) ↔ AUC 1.06 (1.01, 1.12) (Increase in gastric pH)	
Proton pump inhibitors		
Omeprazole (20 mg once daily)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c] Omeprazole dosed simultaneously with Harvoni Lansoprazole[e] Rabeprazole[e] Pantoprazole[e] Esomeprazole[e]	Ledipasvir ↓ C_{max} 0.89 (0.61, 1.30) ↓ AUC 0.96 (0.66, 1.39) Sofosbuvir ↔ C_{max} 1.12 (0.88, 1.42) ↔ AUC 1.00 (0.80, 1.25) GS-331007 ↔ C_{max} 1.14 (1.01, 1.29) ↔ AUC 1.03 (0.96, 1.12) (Increase in gastric pH)	Proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with Harvoni. Proton pump inhibitors should not be taken before Harvoni.
ANTIARRHYTHMICS		
Amiodarone	Interaction not studied.	Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with Harvoni (see sections 4.4 and 4.8).
Digoxin	Interaction not studied. *Expected:* ↑ Digoxin ↔ Ledipasvir ↔ Sofosbuvir ↔ GS-331007 (Inhibition of P-gp)	Co-administration of Harvoni with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Harvoni.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
ANTICOAGULANTS		
Dabigatran etexilate	Interaction not studied. *Expected:* ↑ Dabigatran ↔ Ledipasvir ↔ Sofosbuvir ↔ GS-331007 (Inhibition of P-gp)	Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with Harvoni. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.
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 Harvoni.
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Harvoni is contraindicated with carbamazepine, phenobarbital and phenytoin, potent intestinal P-gp inducers (see section 4.3).
Oxcarbazepine	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Harvoni with oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir leading to reduced therapeutic effect of Harvoni. Such co-administration is not recommended (see section 4.4).
ANTIMYCOBACTERIALS		
Rifampicin (600 mg once daily)/ ledipasvir (90 mg single dose)[d]	Interaction not studied. *Expected:* Rifampicin ↔ C_{max} ↔ AUC ↔ C_{min} *Observed:* Ledipasvir ↓ C_{max} 0.65 (0.56, 0.76) ↓ AUC 0.41 (0.36, 0.48) (Induction of P-gp)	Harvoni is contraindicated with rifampicin, a potent intestinal P-gp inducer (see section 4.3).

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d]	Interaction not studied. *Expected:* Rifampicin ↔ C_{max} ↔ AUC ↔ C_{min} *Observed:* Sofosbuvir ↓ C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) GS-331007 ↔ C_{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) (Induction of P-gp)	
Rifabutin Rifapentine	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Harvoni is contraindicated with rifabutin, a potent intestinal P-gp inducer (see section 4.3). Co-administration of Harvoni with rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Harvoni. Such co-administration is not recommended.
HCV PRODUCTS		
Simeprevir (150 mg once daily)/ ledipasvir (30 mg once daily)	Simeprevir ↑ C_{max} 2.61 (2.39, 2.86) ↑ AUC 2.69 (2.44, 2.96) Ledipasvir ↑ C_{max} 1.81 (1.69, 2.94) ↑ AUC 1.92 (1.77, 2.07)	Concentrations of ledipasvir, sofosbuvir and simeprevir are increased when simeprevir is co-administered with Harvoni. Co-administration is not recommended.
Simeprevir[h]	Simeprevir ↔ C_{max} 0.96 (0.71, 1.30) ↔ AUC 0.94 (0.67, 1.33) Sofosbuvir ↑ C_{max} 1.91 (1.26, 2.90) ↑ AUC 3.16 (2.25, 4.44) GS-331007 ↓ C_{max} 0.69 (0.52, 0.93) ↔ AUC 1.09 (0.87, 1.37)	

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
HIV ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600 mg/ 200 mg/ 300 mg/ once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]	Efavirenz ↔ C_{max} 0.87 (0.79, 0.97) ↔ AUC 0.90 (0.84, 0.96) ↔ C_{min} 0.91 (0.83, 0.99) Emtricitabine ↔ C_{max} 1.08 (0.97, 1.21) ↔ AUC 1.05 (0.98, 1.11) ↔ C_{min} 1.04 (0.98, 1.11) Tenofovir ↑ C_{max} 1.79 (1.56, 2.04) ↑ AUC 1.98 (1.77, 2.23) ↑ C_{min} 2.63 (2.32, 2.97) Ledipasvir ↓ C_{max} 0.66 (0.59, 0.75) ↓ AUC 0.66 (0.59, 0.75) ↓ C_{min} 0.66 (0.57, 0.76) Sofosbuvir ↔ C_{max} 1.03 (0.87, 1.23) ↔ AUC 0.94 (0.81, 1.10) GS-331007 ↔ C_{max} 0.86 (0.76, 0.96) ↔ AUC 0.90 (0.83, 0.97) ↔ C_{min} 1.07 (1.02, 1.13)	No dose adjustment of Harvoni or efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is required.
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate (200 mg/ 25 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]	Emtricitabine ↔ C_{max} 1.02 (0.98, 1.06) ↔ AUC 1.05 (1.02, 1.08) ↔ C_{min} 1.06 (0.97, 1.15) Rilpivirine ↔ C_{max} 0.97 (0.88, 1.07) ↔ AUC 1.02 (0.94, 1.11) ↔ C_{min} 1.12 (1.03, 1.21) Tenofovir ↔ C_{max} 1.32 (1.25, 1.39) ↑ AUC 1.40 (1.31, 1.50) ↑ C_{min} 1.91 (1.74, 2.10) Ledipasvir ↔ C_{max} 1.01 (0.95, 1.07) ↔ AUC 1.08 (1.02, 1.15) ↔ C_{min} 1.16 (1.08, 1.25) Sofosbuvir ↔ C_{max} 1.05 (0.93, 1.20) ↔ AUC 1.10 (1.01, 1.21) GS-331007 ↔ C_{max} 1.06 (1.01, 1.11) ↔ AUC 1.15 (1.11, 1.19) ↔ C_{min} 1.18 (1.13, 1.24)	No dose adjustment of Harvoni or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
Abacavir/ lamivudine (600 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]	Abacavir ↔ C_{max} 0.92 (0.87, 0.97) ↔ AUC 0.90 (0.85, 0.94) Lamivudine ↔ C_{max} 0.93 (0.87, 1.00) ↔ AUC 0.94 (0.90, 0.98) ↔ C_{min} 1.12 (1.05, 1.20) Ledipasvir ↔ C_{max} 1.10 (1.01, 1.19) ↔ AUC 1.18 (1.10, 1.28) ↔ C_{min} 1.26 (1.17, 1.36) Sofosbuvir ↔ C_{max} 1.08 (0.85, 1.35) ↔ AUC 1.21 (1.09, 1.35) GS-331007 ↔ C_{max} 1.00 (0.94, 1.07) ↔ AUC 1.05 (1.01, 1.09) ↔ C_{min} 1.08 (1.01, 1.14)	No dose adjustment of Harvoni or abacavir/ lamivudine is required.
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Atazanavir boosted with ritonavir (300 mg/ 100 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]	Atazanavir ↔ C_{max} 1.07 (1.00, 1.15) ↔ AUC 1.33 (1.25, 1.42) ↑ C_{min} 1.75 (1.58, 1.93) Ledipasvir ↑ C_{max} 1.98 (1.78, 2.20) ↑ AUC 2.13 (1.89, 2.40) ↑ C_{min} 2.36 (2.08, 2.67) Sofosbuvir ↔ C_{max} 0.96 (0.88, 1.05) ↔ AUC 1.08 (1.02, 1.15) GS-331007 ↔ C_{max} 1.13 (1.08, 1.19) ↔ AUC 1.23 (1.18, 1.29) ↔ C_{min} 1.28 (1.21, 1.36)	No dose adjustment of Harvoni or atazanavir (ritonavir boosted) is required. For the combination of tenofovir/emtricitabine + atazanavir/ritonavir, please see below.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
Atazanavir boosted with ritonavir (300 mg/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d] Dosed simultaneously[f]	Atazanavir ↔ C_{max} 1.07 (0.99, 1.14) ↔ AUC 1.27 (1.18, 1.37) ↑ C_{min} 1.63 (1.45, 1.84) Ritonavir ↔ C_{max} 0.86 (0.79, 0.93) ↔ AUC 0.97 (0.89, 1.05) ↑ C_{min} 1.45 (1.27, 1.64) Emtricitabine ↔ C_{max} 0.98 (0.94, 1.02) ↔ AUC 1.00 (0.97, 1.04) ↔ C_{min} 1.04 (0.96, 1.12) Tenofovir ↑ C_{max} 1.47 (1.37, 1.58) ↔ AUC 1.35 (1.29, 1.42) ↑ C_{min} 1.47 (1.38, 1.57) Ledipasvir ↑ C_{max} 1.68 (1.54, 1.84) ↑ AUC 1.96 (1.74, 2.21) ↑ C_{min} 2.18 (1.91, 2.50) Sofosbuvir ↔ C_{max} 1.01 (0.88, 1.15) ↔ AUC 1.11 (1.02, 1.21) GS-331007 ↔ C_{max} 1.17 (1.12, 1.23) ↔ AUC 1.31 (1.25, 1.36) ↑ C_{min} 1.42 (1.34, 1.49)	When given with tenofovir disoproxil fumarate used in conjunction with atazanavir/ritonavir, Harvoni increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4). Atazanavir concentrations are also increased, with a risk for an increase in bilirubin levels/icterus. That risk is even higher if ribavirin is used as part of the HCV treatment.
Darunavir boosted with ritonavir (800 mg/ 100 mg once daily)/ ledipasvir (90 mg once daily)[d]	Darunavir ↔ C_{max} 1.02 (0.88, 1.19) ↔ AUC 0.96 (0.84, 1.11) ↔ C_{min} 0.97 (0.86, 1.10) Ledipasvir ↑ C_{max} 1.45 (1.34, 1.56) ↑ AUC 1.39 (1.28, 1.49) ↑ C_{min} 1.39 (1.29, 1.51)	No dose adjustment of Harvoni or darunavir (ritonavir boosted) is required. For the combination of tenofovir/emtricitabine + darunavir/ritonavir, please see below.
Darunavir boosted with ritonavir (800 mg/ 100 mg once daily)/ sofosbuvir (400 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) GS-331007 ↔ C_{max} 0.97 (0.90, 1.05) ↔ AUC 1.24 (1.18, 1.30)	

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
Darunavir boosted with ritonavir (800 mg/ 100 mg once daily) + emtricitabine/ tenofovir disoproxil fumarate (200 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d] Dosed simultaneously[f]	Darunavir ↔ C_{max} 1.01 (0.96, 1.06) ↔ AUC 1.04 (0.99, 1.08) ↔ C_{min} 1.08 (0.98, 1.20) Ritonavir ↔ C_{max} 1.17 (1.01, 1.35) ↔ AUC 1.25 (1.15, 1.36) ↑ C_{min} 1.48 (1.34, 1.63) Emtricitabine ↔ C_{max} 1.02 (0.96, 1.08) ↔ AUC 1.04 (1.00, 1.08) ↔ C_{min} 1.03 (0.97, 1.10) Tenofovir ↑ C_{max} 1.64 (1.54, 1.74) ↑ AUC 1.50 (1.42, 1.59) ↑ C_{min} 1.59 (1.49, 1.70) Ledipasvir ↔ C_{max} 1.11 (0.99, 1.24) ↔ AUC 1.12 (1.00, 1.25) ↔ C_{min} 1.17 (1.04, 1.31) Sofosbuvir ↓ C_{max} 0.63 (0.52, 0.75) ↓ AUC 0.73 (0.65, 0.82) GS-331007 ↔ C_{max} 1.10 (1.04, 1.16) ↔ AUC 1.20 (1.16, 1.24) ↔ C_{min} 1.26 (1.20, 1.32)	When given with darunavir/ritonavir used in conjunction with tenofovir disoproxil fumarate, Harvoni increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Lopinavir boosted with ritonavir + emtricitabine/ tenofovir disoproxil fumarate	Interaction not studied. *Expected:* ↑ Lopinavir ↑ Ritonavir ↔ Emtricitabine ↑ Tenofovir ↑ Ledipasvir ↔ Sofosbuvir ↔ GS-331007	When given with lopinavir/ritonavir used in conjunction with tenofovir disoproxil fumarate, Harvoni is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Tipranavir boosted with ritonavir	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Harvoni with tipranavir (ritonavir boosted) is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect of Harvoni. Co-administration is not recommended.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
HIV ANTIVIRAL AGENTS: INTEGRASE INHIBITORS		
Raltegravir (400 mg twice daily)/ ledipasvir (90 mg once daily)[d]	Raltegravir ↓ C_{max} 0.82 (0.66, 1.02) ↔ AUC 0.85 (0.70, 1.02) ↑ C_{min} 1.15 (0.90, 1.46) Ledipasvir ↔ C_{max} 0.92 (0.85, 1.00) ↔ AUC 0.91 (0.84, 1.00) ↔ C_{min} 0.89 (0.81, 0.98)	No dose adjustment of Harvoni or raltegravir is required.
Raltegravir (400 mg twice daily)/ sofosbuvir (400 mg once daily)[d]	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) GS-331007 ↔ C_{max} 1.09 (0.99, 1.19) ↔ AUC 1.02 (0.97, 1.08)	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (150 mg/ 150 mg/ 200 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c]	Interaction not studied. *Expected:* ↔ Emtricitabine ↑ Tenofovir *Observed:* Elvitegravir ↔ C_{max} 0.88 (0.82, 0.95) ↔ AUC 1.02 (0.95, 1.09) ↑ C_{min} 1.36 (1.23, 1.49) Cobicistat ↔ C_{max} 1.25 (1.18, 1.32) ↑ AUC 1.59 (1.49, 1.70) ↑ C_{min} 4.25 (3.47, 5.22) Ledipasvir ↑ C_{max} 1.63 (1.51, 1.75) ↑ AUC 1.78 (1.64, 1.94) ↑ C_{min} 1.91 (1.76, 2.08) Sofosbuvir ↑ C_{max} 1.33 (1.14, 1.56) ↑ AUC 1.36 (1.21, 1.52) GS-331007 ↑ C_{max} 1.33 (1.22, 1.44) ↑ AUC 1.44 (1.41, 1.48) ↑ C_{min} 1.53 (1.47, 1.59)	When given with elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate, Harvoni is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Harvoni and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Dolutegravir	Interaction not studied. *Expected:* ↔ Dolutegravir ↔ Ledipasvir ↔ Sofosbuvir ↔ GS-331007	No dose adjustment required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
HERBAL SUPPLEMENTS		
St. John's wort	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Harvoni is contraindicated with St. John's wort, a potent intestinal P-gp inducer (see section 4.3).
HMG-CoA REDUCTASE INHIBITORS		
Rosuvastatin[g]	↑ Rosuvastatin (Inhibition of drug transporters OATP and BCRP)	Co-administration of Harvoni with rosuvastatin may significantly increase the concentration of rosuvastatin (several fold-increase in AUC) which is associated with increased risk of myopathy, including rhabdomyolysis. Co-administration of Harvoni with rosuvastatin is contraindicated (see section 4.3).
Pravastatin[g]	↑ Pravastatin	Co-administration of Harvoni with pravastatin may significantly increase the concentration of pravastatin which is associated with increased risk of myopathy. Clinical and biochemical control is recommended in these patients and a dose adjustment may be needed (see section 4.4).
Other statins	*Expected:* ↑ Statins	Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with Harvoni, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 4.4).
NARCOTIC ANALGESICS		
Methadone	Interaction not studied. *Expected:* ↔ Ledipasvir	No dose adjustment of Harvoni or methadone is required.
Methadone (Methadone maintenance therapy [30 to 130 mg/daily])/ sofosbuvir (400 mg once daily)[d]	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 (0.68, 1.33) ↑ AUC 1.30 (1.00, 1.69) GS-331007 ↓ C_{max} 0.73 (0.65, 0.83) ↔ AUC 1.04 (0.89, 1.22)	
IMMUNOSUPPRESSANTS		
Ciclosporin[g]	Interaction not studied. *Expected:* ↑ Ledipasvir ↔ Ciclosporin	No dose adjustment of Harvoni or ciclosporin is required.

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min} [a, b]**	**Recommendation concerning co-administration with Harvoni**
Ciclosporin (600 mg single dose)/ sofosbuvir (400 mg single dose)[h]	Ciclosporin ↔ C_{max} 1.06 (0.94, 1.18) ↔ AUC 0.98 (0.85, 1.14) Sofosbuvir ↑ C_{max} 2.54 (1.87, 3.45) ↑ AUC 4.53 (3.26, 6.30) GS-331007 ↓ C_{max} 0.60 (0.53, 0.69) ↔ AUC 1.04 (0.90, 1.20)	
Tacrolimus	Interaction not studied. *Expected:* ↔ Ledipasvir	No dose adjustment of Harvoni or tacrolimus is required.
Tacrolimus (5 mg single dose)/ sofosbuvir (400 mg single dose)[h]	Tacrolimus ↓ C_{max} 0.73 (0.59, 0.90) ↑ AUC 1.09 (0.84, 1.40) Sofosbuvir ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) GS-331007 ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13)	
ORAL CONTRACEPTIVES		
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ ledipasvir (90 mg once daily)[d]	Norelgestromin ↔ C_{max} 1.02 (0.89, 1.16) ↔ AUC 1.03 (0.90, 1.18) ↔ C_{min} 1.09 (0.91, 1.31) Norgestrel ↔ C_{max} 1.03 (0.87, 1.23) ↔ AUC 0.99 (0.82, 1.20) ↔ C_{min} 1.00 (0.81, 1.23) Ethinyl estradiol ↑ C_{max} 1.40 (1.18, 1.66) ↔ AUC 1.20 (1.04, 1.39) ↔ C_{min} 0.98 (0.79, 1.22)	No dose adjustment of oral contraceptives is required.
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily)[d]	Norelgestromin ↔ C_{max} 1.07 (0.94, 1.22) ↔ AUC 1.06 (0.92, 1.21) ↔ C_{min} 1.07 (0.89, 1.28) Norgestrel ↔ C_{max} 1.18 (0.99, 1.41) ↑ AUC 1.19 (0.98, 1.45) ↑ C_{min} 1.23 (1.00, 1.51) Ethinyl estradiol ↔ C_{max} 1.15 (0.97, 1.36) ↔ AUC 1.09 (0.94, 1.26) ↔ C_{min} 0.99 (0.80, 1.23)	

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00.
b. All interaction studies conducted in healthy volunteers.
c. Administered as Harvoni.
d. Lack of pharmacokinetics interaction bounds 70-143%.
e. These are drugs within class where similar interactions could be predicted.
f. Staggered administration (12 hours apart) of atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate or darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate and Harvoni provided similar results.
g. This study was conducted in the presence of another two direct-acting antiviral agents.
h. Bioequivalence/Equivalence boundary 80-125%.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females
When Harvoni is used in combination with 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. 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 ledipasvir, sofosbuvir or Harvoni in pregnant women.

Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. No significant effects on foetal development have been observed with ledipasvir or sofosbuvir in rats and rabbits. 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 Harvoni during pregnancy.

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

Available pharmacokinetic data in animals has shown excretion of ledipasvir and metabolites of sofosbuvir in milk (see section 5.3).

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

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

If ribavirin is co-administered with Harvoni, the contraindications regarding use of ribavirin during pregnancy and breast-feeding apply (see also the Summary of Product Characteristics for ribavirin).

4.7 Effects on ability to drive and use machines

Harvoni (administered alone or in combination with ribavirin) has no or negligible influence on the ability to drive and use machines. However, patients should be advised that fatigue was more common in patients treated with ledipasvir/sofosbuvir compared to placebo.

4.8 Undesirable effects

Summary of the safety profile
The safety assessment of ledipasvir/sofosbuvir is based on pooled data from three Phase 3 clinical studies (ION-3, ION-1 and ION-2) including 215, 539 and 326 patients who received ledipasvir/sofosbuvir for 8, 12 and 24 weeks, respectively; and 216, 328 and 328 patients who received ledipasvir/sofosbuvir + ribavirin combination therapy for 8, 12 and 24 weeks, respectively. These studies did not include any control group not receiving ledipasvir/sofosbuvir. Further data include a double-blind comparison of the safety of ledipasvir/sofosbuvir (12 weeks) and placebo in 155 cirrhotic patients (see section 5.1).

The proportion of patients who permanently discontinued treatment due to adverse events was 0%, < 1% and 1% for patients receiving ledipasvir/sofosbuvir for 8, 12 and 24 weeks, respectively; and < 1%, 0%, and 2% for patients receiving ledipasvir/sofosbuvir + ribavirin combination therapy for 8, 12 and 24 weeks, respectively.

In clinical studies, fatigue and headache were more common in patients treated with ledipasvir/sofosbuvir compared to placebo. When ledipasvir/sofosbuvir was studied with ribavirin, the most frequent adverse drug reactions to ledipasvir/sofosbuvir + ribavirin combination therapy were consistent with the known safety profile of ribavirin, without increasing the frequency or severity of the expected adverse drug reactions.

The following adverse drug reactions have been identified with Harvoni (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 Harvoni

Frequency	**Adverse drug reaction**
Nervous system disorders:	
Very common	headache
Skin and subcutaneous tissue disorders:	
Common	rash
General disorders:	
Very common	fatigue

Patients with decompensated cirrhosis and/or who are awaiting liver transplant or post-liver transplant
The safety profile of ledipasvir/sofosbuvir with ribavirin for 12 or 24 weeks in patients with decompensated liver disease and/or those post-liver transplant was assessed in an open-label study (SOLAR-1). No new adverse drug reactions were detected among patients with decompensated cirrhosis and/or who were post-liver transplant and who received ledipasvir/sofosbuvir with ribavirin. Although adverse events, including serious adverse events, occurred more frequently in this study compared to studies that excluded decompensated patients and/or patients who were post-liver transplantation, the adverse events observed were those expected as clinical sequelae of advanced liver disease and/or transplantation or were consistent with the known safety profile of ribavirin (see section 5.1 for details of this study).

Decreases in haemoglobin to < 10 g/dL and < 8.5 g/dL during treatment were experienced by 39% and 13% of patients treated with ledipasvir/sofosbuvir with ribavirin, respectively. Ribavirin was discontinued in 19% of the patients.

10% of liver transplant recipients had a modification of their immunosuppressive agents.

Paediatric population
The safety and efficacy of Harvoni in children and adolescents aged less than 18 years have not yet been established. No data are available.

Description of selected adverse reactions
Cardiac arrhythmias
Cases of severe bradycardia and heart block have been observed when Harvoni is used with concomitant amiodarone and/or other drugs that lower heart rate (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest documented doses of ledipasvir and sofosbuvir were 120 mg twice daily for 10 days and a single dose of 1,200 mg, respectively. In these healthy volunteer studies, there were no untoward effects observed at these dose levels, and adverse reactions were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses are not known.

No specific antidote is available for overdose with Harvoni. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Harvoni consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis is unlikely to result in significant removal of ledipasvir as ledipasvir is highly bound to plasma protein. Haemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AX65

Mechanism of action
Ledipasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. Biochemical confirmation of NS5A inhibition by ledipasvir is not currently possible as NS5A has no enzymatic function. *In vitro* resistance selection and cross-resistance studies indicate ledipasvir targets NS5A as its mode 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 analogue triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity
The EC_{50} values of ledipasvir and sofosbuvir against full-length or chimeric replicons encoding NS5A and NS5B sequences from clinical isolates are detailed in Table 5. The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir but reduced the anti-HCV activity of ledipasvir by 12-fold against genotype 1a HCV replicons.

Table 5: Activity of ledipasvir and sofosbuvir against chimeric replicons

Genotype replicons	Ledipasvir activity (EC_{50}, nM)		Sofosbuvir activity (EC_{50}, nM)	
	Stable replicons	NS5A transient replicons Median (range)[a]	Stable replicons	NS5B transient replicons Median (range)[a]
Genotype 1a	0.031	0.018 (0.009-0.085)	40	62 (29-128)
Genotype 1b	0.004	0.006 (0.004-0.007)	110	102 (45-170)
Genotype 2a	21-249	-	50	29 (14-81)
Genotype 2b	16-530[b]	-	15[b]	-
Genotype 3a	168	-	50	81 (24-181)
Genotype 4a	0.39	-	40	-
Genotype 4d	0.60	-	-	-
Genotype 5a	0.15[b]	-	15[b]	-
Genotype 6a	1.1[b]	-	14[b]	-
Genotype 6e	264[b]	-	-	-

a. Transient replicons carrying NS5A or NS5B from patient isolates.
b. The chimeric replicons carrying NS5A genes from genotype 2b, 5a, 6a and 6e were used for testing ledipasvir while the chimeric replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing sofosbuvir.

Resistance

In cell culture

HCV replicons with reduced susceptibility to ledipasvir have been selected in cell culture for genotype 1a and 1b. Reduced susceptibility to ledipasvir was associated with the primary NS5A substitution Y93H in both genotype 1a and 1b. Additionally a Q30E substitution developed in genotype 1a replicons. Site-directed mutagenesis of NS5A RAVs showed that substitutions conferring a fold-change > 100 and ≤ 1,000 in ledipasvir susceptibility are Q30H/R, L31I/M/V, P32L and Y93T in genotype 1a and P58D and Y93S in genotype 1b; and substitutions conferring a fold-change > 1,000 are M28A/G, Q30E/G/K, H58D, Y93C/H/N/S in genotype 1a and A92K and Y93H in genotype 1b.

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 viral replication capacity by 89% to 99% compared to the corresponding wild-type.

In clinical studies – Genotype 1

In a pooled analysis of patients who received ledipasvir/sofosbuvir in Phase 3 studies (ION-3, ION-1 and ION-2), 37 patients (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA > 1,000 IU/mL. Post-baseline NS5A and NS5B deep sequencing data (assay cut off of 1%) were available for 37/37 and 36/37 patients, respectively.

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients (22/29 genotype 1a and 7/8 genotype 1b) not achieving sustained virologic response (SVR). Of the 29 genotype 1a patients who qualified for resistance testing, 22/29 (76%) patients harboured one or more NS5A RAVs at positions K24, M28, Q30, L31, S38 and Y93 at failure, while the remaining 7/29 patients had no NS5A RAVs detected at failure. The most common variants were Q30R, Y93H and L31M. Of the 8 genotype 1b patients who qualified for resistance testing, 7/8 (88%) harboured one or more NS5A RAVs at positions L31 and Y93 at failure, while 1/8 patients had no NS5A RAVs at failure. The most common variant was Y93H. Among the 8 patients who had no NS5A RAVs at failure, 7 patients received 8 weeks of treatment (n = 3 with ledipasvir/sofosbuvir; n = 4 with ledipasvir/sofosbuvir + ribavirin) and 1 patient received ledipasvir/sofosbuvir for 12 weeks. In phenotypic analyses, post-baseline isolates from patients who harboured NS5A RAVs at failure showed 20- to at least a 243-fold (the highest dose tested) reduced susceptibility to ledipasvir. Site-directed mutagenesis of the Y93H substitution in both genotype 1a and 1b as well as the Q30R

and L31M substitution in genotype 1a conferred high levels of reduced susceptibility to ledipasvir (fold-change in EC_{50} ranging from 544-fold to 1,677-fold).

The sofosbuvir resistance-associated substitution S282T in NS5B was not detected in any virologic failure isolate from the Phase 3 studies. However, the NS5B S282T substitution in combination with NS5A substitutions L31M, Y93H and Q30L were detected in one patient at failure following 8 weeks of treatment with ledipasvir/sofosbuvir from a Phase 2 study (LONESTAR). This patient was subsequently retreated with ledipasvir/sofosbuvir + ribavirin for 24 weeks and achieved SVR following retreatment.

In the SIRIUS study (see "Clinical efficacy and safety", below) 5 patients with genotype 1 infection relapsed after treatment with ledipasvir/sofosbuvir with or without ribavirin. NS5A RAVs were seen at relapse in 5/5 patients (for genotype 1a: Q30R/H + L31M/V [n = 1] and Q30R [n = 1]; for genotype 1b: Y93H [n = 3]).

In the SOLAR-1 study (see "Clinical efficacy and safety", below) 13 patients with genotype 1 infection relapsed after treatment with ledipasvir/sofosbuvir with ribavirin. NS5A RAVs were seen at the time of relapse in 11/13 patients (for genotype 1a: Q30R alone [n = 2], Y93C [n = 1], Y93H/C [n = 2], Q30R + H58D [n = 1], M28T + Q30H [n = 1]; for genotype 1b: Y93H [n = 3], Y93H/C [n = 1]).

In clinical studies – Genotype 2, 3, 4, 5 and 6
NS5A RAVs: No genotype 2 infected patients experienced relapse in the clinical study and therefore there are no data regarding NS5A RAVs at the time of failure.

In genotype 3 infected patients experiencing virologic failure, development of NS5A RAVs (including enrichment of RAVs present at baseline) was typically not detected at the time of failure (n = 17).

In genotype 4, 5 and 6 infection, only small numbers of patients have been evaluated (total of 5 patients with failure). The NS5A substitution Y93C emerged in the HCV of 1 patient (genotype 4), while NS5A RAVs present at baseline were observed at the time of failure in all patients.

NS5B RAVs: The NS5B substitution S282T emerged in the HCV of 1/17 genotype 3-failures, and in the HCV of 1/3, 1/1 and 1/1 of genotype 4-, 5- and 6-failures, respectively.

Effect of baseline HCV resistance-associated variants on treatment outcome
Genotype 1
Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome. In the pooled analysis of the Phase 3 studies, 16% of patients had baseline NS5A RAVs identified by population or deep sequencing irrespective of subtype. Baseline NS5A RAVs were overrepresented in patients who experienced relapse in the Phase 3 studies (see "Clinical efficacy and safety").

Following 12 weeks of treatment with ledipasvir/sofosbuvir (without ribavirin) in treatment-experienced patients (arm 1 of ION-2 study) 4/4 patients with baseline NS5A RAVs conferring a ledipasvir fold-change of ≤ 100 achieved SVR. For the same treatment arm, patients with baseline NS5A RAVs conferring a fold-change of > 100, relapse occurred in 4/13 (31%), as compared to 3/95 (3%) in those without any baseline RAVs or RAVs conferring a fold-change of ≤ 100.

Following 12 weeks of treatment with ledipasvir/sofosbuvir with ribavirin in treatment-experienced patients with compensated cirrhosis (SIRIUS, n = 77), 8/8 patients with baseline NS5A RAVs conferring > 100-fold reduced susceptibility to ledipasvir achieved SVR12.

The group of NS5A RAVs that conferred > 100-fold shift and was observed in patients were the following substitutions in genotype 1a (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C) or in genotype 1b (Y93H). The proportion of such baseline NS5A RAVs seen with deep sequencing varied from very low (cut off for assay = 1%) to high (main part of the plasma population).

The sofosbuvir resistance-associated substitution S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 studies by population or deep sequencing. SVR was achieved in all 24 patients (n = 20 with L159F+C316N; n = 1 with L159F; and n = 3 with N142T) who had baseline variants associated with resistance to NS5B nucleoside inhibitors.

Following treatment with ledipasvir/sofosbuvir with ribavirin for 12 weeks in post-liver transplant patients with compensated liver disease (SOLAR-1), none (n = 8) of the patients with baseline NS5A RAVs conferring a ledipasvir fold-change of > 100 relapsed. Following treatment with ledipasvir/sofosbuvir with ribavirin for 12 weeks in patients with decompensated disease (irrespective of liver transplantation status), 3/7 patients with baseline NS5A RAVs conferring > 100-fold reduced susceptibility to ledipasvir relapsed, as compared to 4/68 in those without any baseline RAVs or RAVs conferring ≤ 100-fold reduced susceptibility to ledipasvir.

Genotype 2, 3, 4, 5 and 6
Due to the limited size of studies, the impact of baseline NS5A RAVs on treatment outcome for patients with genotype 2, 3, 4, 5 or 6 CHC has not been fully evaluated. No major differences in outcomes were observed by the presence or absence of baseline NS5A RAVs.

Cross-resistance
Ledipasvir was fully active against the sofosbuvir resistance-associated substitution S282T in NS5B while all ledipasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and ledipasvir were fully active against substitutions associated with resistance to other classes of direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. NS5A substitutions conferring resistance to ledipasvir may reduce the antiviral activity of other NS5A inhibitors.

Clinical efficacy and safety
The efficacy of Harvoni (ledipasvir [LDV]/sofosbuvir [SOF]) was evaluated in three open-label Phase 3 studies with data available for a total of 1,950 patients with genotype 1 CHC. The three Phase 3 studies included one study conducted in non-cirrhotic treatment-naïve patients (ION-3); one study in cirrhotic and non-cirrhotic treatment-naïve patients (ION-1); and one study in cirrhotic and non-cirrhotic patients who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor (ION-2). Patients in these studies had compensated liver disease. All three Phase 3 studies evaluated the efficacy of ledipasvir/sofosbuvir with or without ribavirin.

Treatment duration was fixed in each study. Serum 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. SVR was the primary endpoint to determine the HCV cure rate which was defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment.

Treatment-naïve adults without cirrhosis – ION-3 (study 0108) – Genotype 1
ION-3 evaluated 8 weeks of treatment with ledipasvir/sofosbuvir with or without ribavirin and 12 weeks of treatment with ledipasvir/sofosbuvir in treatment-naïve non-cirrhotic patients with genotype 1 CHC. Patients were randomised in a 1:1:1 ratio to one of the three treatment groups and stratified by HCV genotype (1a *versus* 1b).

Table 6: Demographics and baseline characteristics in study ION-3

Patient disposition	**LDV/SOF 8 weeks (n = 215)**	**LDV/SOF+RBV 8 weeks (n = 216)**	**LDV/SOF 12 weeks (n = 216)**	**TOTAL (n = 647)**
Age (years): median (range)	53 (22-75)	51 (21-71)	53 (20-71)	52 (20-75)
Male gender	60% (130)	54% (117)	59% (128)	58% (375)
Race: Black/ African American	21% (45)	17% (36)	19% (42)	19% (123)
White	76% (164)	81% (176)	77% (167)	78% (507)
Genotype 1a	80% (171)	80% (172)	80% (172)	80% (515)[a]
IL28CC genotype	26% (56)	28% (60)	26% (56)	27% (172)
FibroTest-Determined Metavir score[b]				
F0-F1	33% (72)	38% (81)	33% (72)	35% (225)
F2	30% (65)	28% (61)	30% (65)	30% (191)
F3-F4	36% (77)	33% (71)	37% (79)	35% (227)
Not interpretable	< 1% (1)	1% (3)	0% (0)	< 1% (4)

a. One patient in the LDV/SOF 8-week treatment arm did not have a confirmed genotype 1 subtype.
b. Non-missing FibroTest results are mapped to Metavir scores according to: 0-0.31 = F0-F1; 0.32-0.58 = F2; 0.59-1.00 = F3-F4.

Table 7: Response rates in study ION-3

	LDV/SOF 8 weeks (n = 215)	**LDV/SOF+RBV 8 weeks (n = 216)**	**LDV/SOF 12 weeks (n = 216)**
SVR	94% (202/215)	93% (201/216)	96% (208/216)
Outcome for patients without SVR			
On-treatment virologic failure	0/215	0/216	0/216
Relapse[a]	5% (11/215)	4% (9/214)	1% (3/216)
Other[b]	< 1% (2/215)	3% (6/216)	2% (5/216)
Genotype			
Genotype 1a	93% (159/171)	92% (159/172)	96% (165/172)
Genotype 1b	98% (42/43)	95% (42/44)	98% (43/44)

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

The 8-week treatment of ledipasvir/sofosbuvir without ribavirin was non-inferior to the 8-week treatment of ledipasvir/sofosbuvir with ribavirin (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%) and the 12-week treatment of ledipasvir/sofosbuvir (treatment difference -2.3%; 97.5% confidence interval: -7.2% to 3.6%). Among patients with a baseline HCV RNA < 6 million IU/mL, the SVR was 97% (119/123) with 8-week treatment of ledipasvir/sofosbuvir and 96% (126/131) with 12-week treatment of ledipasvir/sofosbuvir.

Table 8: Relapse rates by baseline characteristics in the ION-3 study, virological failure population*

	LDV/SOF 8 weeks (n = 213)	**LDV/SOF+RBV 8 weeks (n = 210)**	**LDV/SOF 12 weeks (n = 211)**
Gender			
Male	8% (10/129)	7% (8/114)	2% (3/127)
Female	1% (1/84)	1% (1/96)	0% (0/84)
IL28 genotype			
CC	4% (2/56)	0% (0/57)	0% (0/54)
Non-CC	6% (9/157)	6% (9/153)	2% (3/157)
Baseline HCV RNA[a]			
HCV RNA < 6 million IU/mL	2% (2/121)	2% (3/136)	2% (2/128)
HCV RNA ≥ 6 million IU/mL	10% (9/92)	8% (6/74)	1% (1/83)

* Patients lost to follow-up or who withdrew consent excluded.
a. HCV RNA values were determined using the Roche TaqMan Assay; a patient's HCV RNA may vary from visit to visit.

Treatment-naïve adults with or without cirrhosis – ION-1 (study 0102) – Genotype 1
ION-1 was a randomised, open-label study that evaluated 12 and 24 weeks of treatment with ledipasvir/sofosbuvir with or without ribavirin in 865 treatment-naïve patients with genotype 1 CHC

including those with cirrhosis (randomised 1:1:1:1). Randomisation was stratified by the presence or absence of cirrhosis and HCV genotype (1a *versus* 1b).

Table 9: Demographics and baseline characteristics in study ION-1

Patient disposition	**LDV/SOF 12 weeks (n = 214)**	**LDV/SOF+ RBV 12 weeks (n = 217)**	**LDV/SOF 24 weeks (n = 217)**	**LDV/SOF+ RBV 24 weeks (n = 217)**	**TOTAL (n = 865)**
Age (years): median (range)	52 (18-75)	52 (18-78)	53 (22-80)	53 (24-77)	52 (18-80)
Male gender	59% (127)	59% (128)	64% (139)	55% (119)	59% (513)
Race: Black/ African American	11% (24)	12% (26)	15% (32)	12% (26)	12% (108)
White	87% (187)	87% (188)	82% (177)	84% (183)	85% (735)
Genotype 1a[a]	68% (145)	68% (148)	67% (146)	66% (143)	67% (582)
IL28CC genotype	26% (55)	35% (76)	24% (52)	34% (73)	30% (256)
FibroTest-Determined Metavir score[b]					
F0-F1	27% (57)	26% (56)	29% (62)	30% (66)	28% (241)
F2	26% (56)	25% (55)	22% (47)	28% (60)	25% (218)
F3-F4	47% (100)	48% (104)	49% (107)	42% (91)	46% (402)
Not interpretable	< 1% (1)	1% (2)	< 1% (1)	0% (0)	< 1% (4)

a. Two patients in the LDV/SOF 12-week treatment arm, one patient in the LDV/SOF+RBV 12-week treatment arm, two patients in the LDV/SOF 24-week treatment arm, and two patients in the LDV/SOF+RBV 24-week treatment arm did not have a confirmed genotype 1 subtype.
b. Non-missing FibroTest results are mapped to Metavir scores according to: 0-0.31 = F0-F1; 0.32-0.58 = F2; 0.59-1.00 = F3-F4.

Table 10: Response rates in study ION-1

	LDV/SOF 12 weeks (n = 214)	**LDV/SOF+RBV 12 weeks (n = 217)**	**LDV/SOF 24 weeks (n = 217)**	**LDV/SOF+RBV 24 weeks (n = 217)**
SVR	99% (210/213)	97% (211/217)	98% (213/217)	99% (215/217)
Outcome for patients without SVR				
On-treatment virologic failure	0/213[a]	0/217	< 1% (1/217)	0/216
Relapse[b]	< 1% (1/212)	0/217	< 1% (1/215)	0/216
Other[c]	< 1% (2/213)	3% (6/217)	< 1% (2/217)	< 1% (2/217)
SVR rates for selected subgroups				
Genotype				
Genotype 1a	98% (142/145)	97% (143/148)	99% (144/146)	99% (141/143)
Genotype 1b	100% (67/67)	99% (67/68)	97% (67/69)	100% (72/72)
Cirrhosis[d]				
No	99% (176/177)	97% (177/183)	98% (181/184)	99% (178/180)
Yes	94% (32/34)	100% (33/33)	97% (32/33)	100% (36/36)

a. One patient was excluded from the LDV/SOF 12-week treatment arm and one patient was excluded from the LDV/SOF+RBV 24-week treatment arm as both patients were infected with genotype 4 CHC.
b. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g. lost to follow-up).
d. Patients with missing cirrhosis status were excluded from this subgroup analysis.

Previously treated adults with or without cirrhosis – ION-2 (study 0109) – Genotype 1
ION-2 was a randomised, open-label study that evaluated 12 and 24 weeks of treatment with ledipasvir/sofosbuvir with or without ribavirin (randomised 1:1:1:1) in genotype 1 HCV-infected patients with or without cirrhosis who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor. Randomisation was stratified by the presence or absence of cirrhosis, HCV genotype (1a *versus* 1b) and response to prior HCV therapy (relapse/breakthrough *versus* non-response).

Table 11: Demographics and baseline characteristics in study ION-2

Patient disposition	LDV/SOF 12 weeks (n = 109)	LDV/SOF+ RBV 12 weeks (n = 111)	LDV/SOF 24 weeks (n = 109)	LDV/SOF+ RBV 24 weeks (n = 111)	TOTAL (n = 440)
Age (years): median (range)	56 (24-67)	57 (27-75)	56 (25-68)	55 (28-70)	56 (24-75)
Male gender	68% (74)	64% (71)	68% (74)	61% (68)	65% (287)
Race: Black/ African American	22% (24)	14% (16)	16% (17)	18% (20)	18% (77)
White	77% (84)	85% (94)	83% (91)	80% (89)	81% (358)
Genotype 1a	79% (86)	79% (88)	78% (85)	79% (88)	79% (347)
Prior HCV therapy					
PEG-IFN+RBV	39% (43)	42% (47)	53% (58)	53% (59)	47% (207)[a]
HCV protease inhibitor + PEG-IFN+RBV	61% (66)	58% (64)	46% (50)	46% (51)	53% (231)[a]
IL28CC genotype	9% (10)	10% (11)	14% (16)	16% (18)	13% (55)
FibroTest-Determined Metavir score[b]					
F0-F1	14% (15)	10% (11)	12% (13)	16% (18)	13% (57)
F2	28% (31)	26% (29)	28% (31)	30% (33)	28% (124)
F3-F4	58% (63)	64% (71)	58% (63)	54% (60)	58% (257)
Not interpretable	0% (0)	0% (0)	2% (2)	0% (0)	< 1% (2)

a. One patient in the LDV/SOF 24-week treatment arms and one patient in the LDV/SOF+RBV 24-week treatment arm were prior treatment failures of a non-pegylated interferon based regimen.
b. Non-missing FibroTest results are mapped to Metavir scores according to: 0-0.31 = F0-F1; 0.32-0.58 = F2; 0.59-1.00 = F3-F4.

Table 12: Response rates in study ION-2

	LDV/SOF 12 weeks (n = 109)	LDV/SOF+RBV 12 weeks (n = 111)	LDV/SOF 24 weeks (n = 109)	LDV/SOF+RBV 24 weeks (n = 111)
SVR	94% (102/109)	96% (107/111)	99% (108/109)	99% (110/111)
Outcome for patients without SVR				
On-treatment virologic failure	0/109	0/111	0/109	< 1% (1/111)
Relapse[a]	6% (7/108)	4% (4/111)	0/109	0/110
Other[b]	0/109	0/111	< 1% (1/109)	0/111
SVR rates for selected subgroups				
Genotype				
Genotype 1a	95% (82/86)	95% (84/88)	99% (84/85)	99% (87/88)
Genotype 1b	87% (20/23)	100% (23/23)	100% (24/24)	100% (23/23)
Cirrhosis				
No	95% (83/87)	100% (88/88)[c]	99% (85/86)[c]	99% (88/89)
Yes[d]	86% (19/22)	82% (18/22)	100% (22/22)	100% (22/22)
Prior HCV therapy				
PEG-IFN+RBV	93% (40/43)	96% (45/47)	100% (58/58)	98% (58/59)
HCV protease inhibitor + PEG-IFN+RBV	94% (62/66)	97% (62/64)	98% (49/50)	100% (51/51)

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g. lost to follow-up).
c. Patients with missing cirrhosis status were excluded from this subgroup analysis.
d. Metavir score = 4 or Ishak score ≥ 5 by liver biopsy, or FibroTest score of > 0.75 and (APRI) of > 2.

Table 13 presents relapse rates with the 12-week regimens (with or without ribavirin) for selected subgroups (see also previous section "Effect of baseline HCV resistance-associated variants on treatment outcome"). In non-cirrhotic patients relapses only occurred in the presence of baseline NS5A RAVs, and during therapy with ledipasvir/sofosbuvir without ribavirin. In cirrhotic patients relapses occurred with both regimens, and in the absence and presence of baseline NS5A RAVs.

Table 13: Relapse rates for selected subgroups in study ION-2

	LDV/SOF 12 weeks (n = 109)	**LDV/SOF+RBV 12 weeks (n = 111)**	**LDV/SOF 24 weeks (n = 109)**	**LDV/SOF+RBV 24 weeks (n = 111)**
Number of responders at end of treatment	108	111	109	110
Cirrhosis				
No	5% (4/86)[a]	0% (0/88)[b]	0% (0/86)[b]	0% (0/88)
Yes	14% (3/22)	18% (4/22)	0% (0/22)	0% (0/22)
Presence of baseline NS5A resistance-associated substitutions[c]				
No	3% (3/91)[d]	2% (2/94)	0% (0/96)	0% (0/95)[f]
Yes	24% (4/17)[e]	12% (2/17)	0% (0/13)	0% (0/14)

a. These 4 non-cirrhotic relapsers all had baseline NS5A resistance-associated polymorphisms.
b. Patients with missing cirrhosis status were excluded from this subgroup analysis.
c. Analysis (by deep sequencing) included NS5A resistance-associated polymorphisms that conferred > 2.5-fold change in EC_{50} (K24G/N/R, M28A/G/T, Q30E/G/H/L/K/R/T, L31I/F/M/V, P32L, S38F, H58D, A92K/T, and Y93C/F/H/N/S for genotype 1a and L31I/F/M/V, P32L, P58D, A92K, and Y93C/H/N/S for genotype 1b HCV infection).
d. 3/3 of these patients had cirrhosis.
e. 0/4 of these patients had cirrhosis.
f. One patient who achieved a viral load < LLOQ at end of treatment had missing baseline NS5A data and was excluded from the analysis.

Previously treated adults with cirrhosis – SIRIUS – Genotype 1
SIRIUS included patients with compensated cirrhosis who first failed therapy with pegylated interferon (PEG-IFN) + ribavirin, and then failed a regimen consisting of a pegylated interferon + ribavirin + an NS3/4A protease inhibitor. Cirrhosis was defined by biopsy, Fibroscan (> 12.5 kPa) or FibroTest > 0.75 and an AST:platelet ratio index (APRI) of > 2.

The study (double-blind and placebo-controlled) evaluated 24 weeks of treatment ledipasvir/sofosbuvir (with ribavirin placebo) *versus* 12 weeks of treatment with ledipasvir/sofosbuvir with ribavirin. Patients in the latter treatment arm received placebo (for ledipasvir/sofosbuvir and ribavirin) during the first 12 weeks, followed by active blinded therapy during the subsequent 12 weeks. Patients were stratified by HCV genotype (1a *versus* 1b) and prior treatment response (whether HCV RNA < LLOQ had been achieved).

Demographics and baseline characteristics were balanced across the two treatment groups. The median age was 56 years (range: 23 to 77); 74% of patients were male; 97% were white; 63% had genotype 1a HCV infection; 94% had non-CC IL28B alleles (CT or TT).

Of the 155 patients enrolled, 1 patient discontinued treatment whilst on placebo. Of the remaining 154 patients, a total of 149 achieved SVR12 across both treatment groups; 96% (74/77) of patients in the ledipasvir/sofosbuvir with ribavirin 12-week group and 97% (75/77) of patients in the ledipasvir/sofosbuvir 24-week group. All 5 patients who did not achieve SVR12 relapsed after having end-of-treatment response (see section "Resistance" – "In clinical studies" above).

Previously treated adults who have failed on sofosbuvir + ribavirin ± PEG-IFN
The efficacy of ledipasvir/sofosbuvir in patients who had previously failed treatment with sofosbuvir + ribavirin ± PEG-IFN is supported by two clinical studies. In study 1118, 44 patients with genotype 1 infection, including 12 cirrhotic patients, who had previously failed treatment with sofosbuvir + ribavirin + PEG-IFN or with sofosbuvir + ribavirin were treated with ledipasvir/sofosbuvir + ribavirin for 12 weeks; the SVR was 100% (44/44). In study ION-4, 13 HCV/HIV-1 co-infected patients with genotype 1, including 1 cirrhotic patient, who had failed a sofosbuvir + ribavirin regimen were enrolled; the SVR was 100% (13/13) after 12 weeks of treatment with ledipasvir/sofosbuvir.

HCV/HIV co-infected adults – ION-4
ION-4 was an open-label clinical study that evaluated the safety and efficacy of 12 weeks of treatment with ledipasvir/sofosbuvir without ribavirin in HCV treatment-naïve and treatment-experienced patients with genotype 1 or 4 CHC who were co-infected with HIV-1. Treatment-experienced patients had failed prior treatment with PEG-IFN + ribavirin ± an HCV protease inhibitor or sofosbuvir +

ribavirin ± PEG-IFN. Patients were on a stable HIV-1 antiretroviral therapy that included emtricitabine/tenofovir disoproxil fumarate, administered with efavirenz, rilpivirine or raltegravir.

The median age was 52 years (range: 26 to 72); 82% of the patients were male; 61% were white; 34% were black; 75% had genotype 1a HCV infection; 2% had genotype 4 infection; 76% had non-CC IL28B alleles (CT or TT); and 20% had compensated cirrhosis. Fifty-five percent (55%) of the patients were treatment-experienced.

Table 14: Response rates in study ION-4

	LDV/SOF 12 weeks (n = 335)
SVR	96% (321/335)[a]
Outcome for patients without SVR	
On-treatment virologic failure	< 1% (2/335)
Relapse[b]	3% (10/333)
Other[c]	< 1% (2/335)
SVR rates for selected subgroups	
Patients with cirrhosis	94% (63/67)
Previously treated patients with cirrhosis	98% (46/47)

a. 8 patients with genotype 4 HCV infection were enrolled in the study with 8/8 achieving SVR12.
b. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g. lost to follow-up).

HCV/HIV co-infected adults – ERADICATE
ERADICATE was an open-label study to evaluate 12 weeks of treatment with ledipasvir/sofosbuvir in 50 patients with genotype 1 CHC co-infected with HIV. All patients were treatment-naïve to HCV therapy without cirrhosis, 26% (13/50) of patients were HIV antiretroviral naïve and 74% (37/50) of patients were receiving concomitant HIV antiretroviral therapy. At the time of the interim analysis 40 patients have reached 12 weeks post treatment and SVR12 was 98% (39/40).

Patients awaiting liver transplantation and post-liver transplant – SOLAR-1
SOLAR-1 is an open-label, multicentre study evaluating 12 and 24 weeks of treatment with ledipasvir/sofosbuvir + ribavirin in patients with genotype 1 or 4 CHC who have advanced liver disease and/or who have undergone liver transplantation. Seven patient populations are being evaluated (patients with decompensated cirrhosis [CPT B and C] pre-transplant; post-transplant, no cirrhosis; post-transplant CPT A; post-transplant CPT B; post-transplant CPT C; post-transplant fibrosing cholestatic hepatitis [FCH]). Patients with a CPT score > 12 were excluded.

Table 15: Response rates (SVR12) in study SOLAR-1

	LDV/SOF+RBV 12 weeks (n = 168)[a]		**LDV/SOF+RBV 24 weeks (n = 163)[a]**	
	SVR	**Relapse**	**SVR**	**Relapse**
Pre-transplant				
CPT B	87% (26/30)	10.3% (3/29)	89% (24/27)	4.0% (1/25)
CPT C	86% (19/22)	5.0% (1/20)	87% (20/23)	9.1% (2/22)
Post-transplant				
Metavir score F0-F3	96% (53/55)	3.6% (2/55)	98% (55/56)	0% (0/55)
CPT A[b]	96% (25/26)	0% (0/25)	96% (24/25)	0% (0/24)
CPT B[b]	85% (22/26)	4.3% (1/23)	88% (23/26)	0% (0/23)
CPT C[b]	60% (3/5)	40.0% (2/5)	75% (3/4)	25% (1/4)
FCH	100% (4/4)	0% (0/4)	100% (2/2)	0% (0/2)

a. Six patients (1 in the 12-week, 5 in the 24-week treatment group) with HCV RNA < LLOQ at last measurement prior to transplant, were transplanted prior to SVR12 and were excluded from SVR12 and relapse analyses. Only patients who demonstrated SVR12 or relapse were included in relapse analyses.
b. CPT = Child-Pugh-Turcotte. CPT A = CPT score 5-6 (compensated), CPT B = CPT score 7-9 (decompensated), CPT C = CPT score 10-12 (decompensated).

Of 169 patients with decompensated cirrhosis (pre- or post-transplant CPT B or C), those patients who achieved SVR12 and had post-treatment week 12 laboratory data available (e.g. excluding patients who died, were transplanted, or had missing data at this time-point) were assessed for changes in their MELD and CPT scores.

Change in MELD score: 53% (72/135) and 21% (28/135) had an improvement or no change of MELD score from baseline to post-treatment week 4, respectively; of the 35 patients whose MELD score was ≥ 15 at baseline, 63% (22/35) had a MELD score < 15 at post-treatment week 12. The improvement in MELD scores observed was driven largely by improvements in total bilirubin.

Change in CPT: 59% (79/133) and 34% (45/133) had an improvement or no change of CPT scores from baseline to post-treatment week 12, respectively; of the 39 patients who had CPT C cirrhosis at baseline, 56% (22/39) had CPT B cirrhosis at post-treatment week 12; of the 99 patients who had CPT B cirrhosis at baseline, 29% (27/92) had CPT A cirrhosis at post-treatment week 12. The improvement in CPT scores observed was driven largely by improvements in total bilirubin and albumin.

Clinical efficacy and safety in genotype 2, 3, 4, 5 and 6 (see also section 4.4)
Ledipasvir/sofosbuvir has been evaluated for the treatment of non-genotype 1 infection in small Phase 2 studies, as summarised below.

The clinical studies enrolled patients with or without cirrhosis, who were treatment-naïve or with prior treatment failure after therapy with PEG-IFN + ribavirin +/- an HCV protease inhibitor.

For genotype 2, 4, 5 and 6 infection, therapy consisted of ledipasvir/sofosbuvir without ribavirin, given for 12 weeks (Table 16). For genotype 3 infection, ledipasvir/sofosbuvir was given with or without ribavirin, also for 12 weeks (Table 17).

Table 16: Response rates (SVR12) with ledipasvir/sofosbuvir for 12 weeks in patients with genotype 2, 4, 5 and 6 HCV infection

Study	GT	n	TE[a]	SVR12		Relapse[b]
				Overall	Cirrhosis	
Study 1468 (LEPTON)	2	26	19% (5/26)	96% (25/26)	100% (2/2)	0% (0/25)
Study 1119	4	44	50% (22/44)	93% (41/44)	100% (10/10)	7% (3/44)
Study 1119	5	41	49% (20/41)	93% (38/41)	89% (8/9)	5% (2/40)
Study 0122 (ELECTRON-2)	6	25	0% (0/25)	96% (24/25)	100% (2/2)	4% (1/25)

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

Table 17: Response rates (SVR12) in patients with genotype 3 infection (ELECTRON-2)

	LDV/SOF+RBV 12 weeks		LDV/SOF 12 weeks	
	SVR	Relapse[a]	SVR	Relapse[a]
Treatment-naïve	100% (26/26)	0% (0/26)	64% (16/25)	33% (8/24)
Patients without cirrhosis	100% (20/20)	0% (0/21)	71% (15/21)	25% (5/20)
Patients with cirrhosis	100% (6/6)	0% (0/5)	25% (1/4)	75% (3/4)
Treatment-experienced	82% (41/50)	16% (8/49)	NS	NS
Patients without cirrhosis	89% (25/28)	7% (2/27)	NS	NS
Patients with cirrhosis	73% (16/22)	27% (6/22)	NS	NS

NS: not studied.
a. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.

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

5.2 Pharmacokinetic properties

Absorption
Following oral administration of ledipasvir/sofosbuvir to HCV-infected patients, ledipasvir median peak plasma concentration was observed at 4.0 hours post-dose. Sofosbuvir was absorbed quickly and the median peak plasma concentrations were observed ~ 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed at 4 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected patients, geometric mean steady-state AUC_{0-24} for ledipasvir (n = 2,113), sofosbuvir (n = 1,542), and GS-331007 (n = 2,113) were 7,290, 1,320 and 12,000 ng•h/mL, respectively. Steady-state C_{max} for ledipasvir, sofosbuvir and GS-331007 were 323, 618 and 707 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection. Relative to healthy subjects (n = 191), ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively, in HCV-infected patients. Ledipasvir AUC is dose proportional over the dose range of 3 to 100 mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 400 mg.

Effects of food
Relative to fasting conditions, the administration of a single dose of ledipasvir/sofosbuvir with a moderate fat or high fat meal increased the sofosbuvir AUC_{0-inf} by approximately 2-fold, but did not significantly affect the sofosbuvir C_{max}. The exposures to GS-331007 and ledipasvir were not altered in the presence of either meal type. Harvoni can be administered without regard to food.

Distribution
Ledipasvir is > 99.8% bound to human plasma proteins. After a single 90 mg dose of [^{14}C]-ledipasvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.51 and 0.66.

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity was approximately 0.7.

Biotransformation
In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [^{14}C]-ledipasvir, systemic exposure was almost exclusively due to the parent drug (> 98%). Unchanged ledipasvir is also the major species present in faeces.

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analogue triphosphate GS-461203. The active metabolite is not observed. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A or carboxylesterase 1 and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. Within ledipasvir/sofosbuvir, GS-331007 accounts for approximately 85% of total systemic exposure.

Elimination
Following a single 90 mg oral dose of [^{14}C]-ledipasvir, mean total recovery of the [^{14}C]-radioactivity in faeces and urine was 87%, with most of the radioactive dose recovered from faeces (86%). Unchanged ledipasvir excreted in faeces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. These data suggest that biliary excretion of unchanged ledipasvir is a major route of elimination with renal excretion being a minor pathway (approximately 1%). The median terminal half-life of ledipasvir in healthy volunteers following administration of ledipasvir/sofosbuvir in the fasted state was 47 hours.

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 following administration of ledipasvir/sofosbuvir were 0.5 and 27 hours, respectively.

Neither ledipasvir nor sofosbuvir are substrates for hepatic uptake transporters, organic cation transporter (OCT) 1, organic anion-transporting polypeptide (OATP) 1B1 or OATP1B3. GS-331007 is not a substrate for renal transporters including organic anion transporter (OAT) 1 or OAT3, or OCT2.

In vitro potential for ledipasvir/sofosbuvir to affect other medicinal products
At concentrations achieved in the clinic, ledipasvir is not an inhibitor of hepatic transporters including the OATP 1B1 or 1B3, BSEP, OCT1, OCT2, OAT1, OAT3, multidrug and toxic compound extrusion (MATE) 1 transporter, multidrug resistance protein (MRP) 2 or MRP4. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OCT1 and GS-331007 is not an inhibitor of OAT1, OCT2 and MATE1.

Sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes.

Pharmacokinetics in special populations
Race and gender
No clinically relevant pharmacokinetic differences due to race have been identified for ledipasvir, sofosbuvir or GS-331007. No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir or GS-331007. AUC and C_{max} of ledipasvir were 77% and 58% higher, respectively, in females than males; however, the relationship between gender and ledipasvir exposures was not considered clinically relevant.

Elderly
Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 80 years) analysed, age did not have a clinically relevant effect on the exposure to ledipasvir, sofosbuvir or GS-331007. Clinical studies of ledipasvir/sofosbuvir included 235 patients (8.6% of total number of patients) aged 65 years and over.

Renal impairment
The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault, median [range] CrCl 22 [17-29] mL/min). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment.

The pharmacokinetics of sofosbuvir were studied in HCV negative patients 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 patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients 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 patients with ESRD, relative to patients 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 patients with ESRD administered with sofosbuvir 1 hour before or 1 hour after haemodialysis was at least 10-fold and 20-fold higher, respectively. GS-331007 is efficiently removed by haemodialysis with an extraction coefficient of approximately 53%. Following a single 400 mg dose of sofosbuvir, a

4 hour haemodialysis removed 18% of administered sofosbuvir dose. The safety and efficacy of sofosbuvir have not been established in patients with severe renal impairment or ESRD.

Hepatic impairment
The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe hepatic impairment (CPT class C). Ledipasvir plasma exposure (AUC_{inf}) was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to ledipasvir.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (CPT class B and C). Relative to patients with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007.

Body weight
Body weight did not have a significant effect on sofosbuvir exposure according to a population pharmacokinetic analysis. Exposure to ledipasvir decreases with increasing body weight but the effect is not considered to be clinically relevant.

Paediatric population
The pharmacokinetics of ledipasvir, sofosbuvir and GS-331007 in paediatric patients have not been established (see section 4.2).

5.3 Preclinical safety data

Ledipasvir
No target organs of toxicity were identified in rat and dog studies with ledipasvir at AUC exposures approximately 7 times the human exposure at the recommended clinical dose.

Ledipasvir 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* rat micronucleus assays.

Ledipasvir was not carcinogenic in the 6-month rasH2 transgenic mouse study at exposures up to 26-fold higher than human exposure. A carcinogenicity study in rats is ongoing.

Ledipasvir had no adverse effects on mating and fertility. In female rats, the mean number of corpora lutea and implantation sites were slightly reduced at maternal exposures 6-fold the exposure in humans at the recommended clinical dose. At the no observed effect level, AUC exposure to ledipasvir was approximately 7- and 3-fold, in males and females, respectively, the human exposure at the recommended clinical dose.

No teratogenic effects were observed in rat and rabbit developmental toxicity studies with ledipasvir.

In a rat pre- and postnatal study, at a maternally toxic dose, the developing rat offspring exhibited mean decreased body weight and body weight gain when exposed *in utero* (via maternal dosing) and during lactation (via maternal milk) at a maternal exposure 4 times the exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioural development and reproductive performance in the offspring at maternal exposures similar to the exposure in humans at the recommended clinical dose.

When administered to lactating rats, ledipasvir was detected in plasma of suckling rats likely due to excretion of ledipasvir via milk.

Sofosbuvir
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 doses which cause adverse effects was 16 times (rat) and 71 times (dog) higher than the clinical exposure at 400 mg sofosbuvir. No liver or heart findings were observed in chronic toxicity studies at exposures 5 times (rat) and 16 times (dog) higher than the clinical exposure. No liver or heart findings were observed in the 2-year carcinogenicity studies at exposures 17 times (mouse) and 9 times (rat) 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 17 times (mouse) and 9 times (rat) higher than the clinical exposure at 400 mg sofosbuvir.

Sofosbuvir had no effects on embryo-foetal viability or on fertility in rat and was not teratogenic in rat and rabbit development studies. No adverse effects on behaviour, reproduction or development of offspring in rat were reported. In rabbit studies exposure to sofosbuvir was 6 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 was approximately 5 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
Copovidone
Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film-coating
Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Talc
Sunset yellow FCF aluminium lake (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Harvoni tablets are supplied in high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure containing 28 film-coated tablets with a silica gel desiccant and polyester coil.

The following pack sizes are available: outer cartons containing 1 bottle of 28 film-coated tablets and outer cartons containing 84 (3 bottles of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd.
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/958/001
EU/1/14/958/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 November 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to evaluate the recurrence of hepatocellular carcinoma associated with Harvoni, the MAH shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol. The final study report shall be submitted by:	Q2 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Harvoni 90 mg/400 mg film-coated tablets
ledipasvir/sofosbuvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 90 mg ledipasvir and 400 mg sofosbuvir.

3. LIST OF EXCIPIENTS

Contains lactose and sunset yellow FCF aluminium lake (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets.
84 (3 bottles of 28) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences International Ltd
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/958/001 28 film-coated tablets
EU/1/14/958/002 84 (3 bottles of 28) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Harvoni [Outer packaging only]

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Harvoni 90 mg/400 mg film-coated tablets
ledipasvir/sofosbuvir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Harvoni is and what it is used for

Harvoni is a medicine that contains the active substances ledipasvir and sofosbuvir in a single tablet. It is given to treat chronic (long-term) hepatitis C virus infection in adults of 18 years and older.

Hepatitis C is a virus that infects the liver. The active substances in the medicine work together by blocking two different proteins that the virus needs to grow and reproduce itself, allowing the infection to be permanently eliminated from the body.

Harvoni is sometimes taken with another medicine, ribavirin.

It is very important that you also read the leaflets for the other medicines that you will be taking with Harvoni. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take Harvoni

Do not take Harvoni
- **If you are allergic** to ledipasvir, sofosbuvir or any of the other ingredients of this medicine (listed in section 6 of this leaflet).

  →If this applies to you, **do not take Harvoni and tell your doctor immediately.**

- **If you are currently taking any of the following medicines:**
  - **rifampicin and rifabutin** (antibiotics used to treat infections, including tuberculosis);
  - **St. John's wort** (*Hypericum perforatum* – herbal medicine used to treat depression);
  - **carbamazepine, phenobarbital and phenytoin** (medicines used to treat epilepsy and prevent seizures);
  - **rosuvastatin** (a medicine used to treat high cholesterol).

Warnings and precautions
Your doctor will know if any of the following conditions apply to you. These will be considered before treatment with Harvoni is started.

- **other liver problems** apart from hepatitis C, for instance
  - **if you are awaiting a liver transplant;**
  - **if you have** a current or previous infection with the **hepatitis B** virus, since your doctor may want to monitor you more closely;
- **kidney problems,** since Harvoni has not been fully tested in patients with severe kidney problems;
- **ongoing treatment for HIV infection,** since your doctor may want to monitor you more closely.

Talk to your doctor or pharmacist before taking Harvoni if:

- you currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats (your doctor may consider alternative treatments if you have taken this medicine).

Tell your doctor immediately if you are taking any medicines for heart problems and during treatment you experience:

- shortness of breath
- light-headedness
- palpitations
- fainting

Blood tests
Your doctor will test your blood before, during and after your treatment with Harvoni. This is so that:

- Your doctor can decide if you should take Harvoni and for how long;
- Your doctor can confirm that your treatment has worked and you are free of the hepatitis C virus.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age. The use of Harvoni in children and adolescents has not yet been studied.

Other medicines and Harvoni
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription.

Warfarin and other similar medicines called vitamin K antagonists used to thin the blood. Your doctor may need to increase the frequency of your blood tests to check how well your blood can clot.

If you are not sure about taking any other medicines, talk to your doctor or pharmacist.

Some medicines should not be taken with Harvoni.

- **Do not take any other medicine that contains sofosbuvir, one of the active substances in Harvoni.**

- **Do not take any of these medicines with Harvoni:**
  - **rifapentine** (antibiotic used to treat infections, including tuberculosis);
  - **oxcarbazepine** (a medicine used to treat epilepsy and prevent seizures);
  - **simeprevir** (a medicine used to treat hepatitis C infection);
  - **tipranavir** (used to treat HIV infection).

Taking Harvoni with any of these may make Harvoni work less well or make any side effects of the medicines worse.

Tell your doctor or pharmacist if you are taking any of the medicines below:

- **amiodarone** used to treat irregular heartbeats;
- **tenofovir disoproxil fumarate** or any medicine containing tenofovir disoproxil fumarate, used to treat HIV infection;
- **digoxin** used to treat heart conditions;
- **dabigatran** used to thin the blood;
- **statins** used to treat high cholesterol.

Taking Harvoni with any of these may stop your medicines from working properly, or make any side effects worse. Your doctor may need to give you a different medicine or adjust the dose of medicine you are taking.

- **Get advice from a doctor or pharmacist** if you take medicines used to treat **stomach ulcers, heartburn or acid reflux.** This includes:
  - antacids (such as aluminium/magnesium hydroxide or calcium carbonate). These should be taken at least 4 hours before or 4 hours after Harvoni;
  - proton pump inhibitors (such as omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole). These should be taken at the same time as Harvoni. Do not take proton pump inhibitors before Harvoni. Your doctor may give you a different medicine or adjust the dose of the medicine you are taking;
  - H_2-receptor antagonists (such as famotidine, cimetidine, nizatidine or ranitidine). Your doctor may give you a different medicine or adjust the dose of the medicine you are taking.

These medicines can decrease the amount of ledipasvir in your blood. If you are taking one of these medicines your doctor will either give you a different medicine for stomach ulcers, heartburn or acid reflux, or recommend how and when you take that medicine.

Pregnancy and contraception
The effects of Harvoni during pregnancy are not known. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy must be avoided if Harvoni is taken together with ribavirin. Ribavirin can be very damaging to an unborn baby. Therefore, you and your partner must take special precautions in sexual activity if there is any chance for pregnancy to occur.

- You or your partner must use an effective birth control method during treatment with Harvoni **together with ribavirin** and for some time afterwards. It is very important that you read the "Pregnancy" section in the ribavirin package leaflet very carefully. Ask your doctor for effective contraceptive method suitable for you.
- If you or your partner become pregnant during Harvoni and ribavirin treatment or in the months that follow, you must contact your doctor immediately.

Breast-feeding
Do not breast-feed during treatment with Harvoni. It is not known whether ledipasvir or sofosbuvir, the two active substances of Harvoni, pass into human breast milk.

Driving and using machines
Do not drive or operate machines if you feel tired after taking your medicine.

Harvoni contains lactose
- **Tell your doctor if you are lactose intolerant or intolerant to other sugars.** Harvoni contains lactose monohydrate. If you are lactose intolerant, or if you have been told that you have an intolerance to other sugars, talk to your doctor before taking this medicine.

Harvoni contains sunset yellow FCF aluminium lake (E110)

- **Tell your doctor if you are allergic** to sunset yellow FCF aluminium lake, also called "E110" before taking this medicine.

3. How to take Harvoni

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose
The recommended dose is **one tablet once a day.** Your doctor will tell you for how many weeks you should take Harvoni.

Swallow the tablet whole with or without food. Do not chew, crush or split the tablet as it has a very bitter taste. Tell your doctor or pharmacist if you have problems swallowing tablets.

If you are taking an antacid, take it at least 4 hours before or at least 4 hours after Harvoni.

If you are taking a proton pump inhibitor, take it at the same time as Harvoni. Do not take it before Harvoni.

If you are sick (vomit) after taking Harvoni it may affect the amount of Harvoni in your blood. This may make Harvoni work less well.

- If you are sick (vomit) **less than 5 hours after** taking Harvoni, take another tablet.
- If you are sick (vomit) **more than 5 hours after** taking Harvoni, you do not need to take another tablet until your next scheduled tablet.

If you take more Harvoni than you should
If you accidentally take more than the recommended dose you should contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Harvoni
It is important not to miss a dose of this medicine.

If you do miss a dose, work out how long it is since you last took your Harvoni:

- **If you notice within 18 hours** of the time you usually take Harvoni, you must take the tablet as soon as possible. Then take the next dose at your usual time.
- **If it's 18 hours or more** after the time you usually take Harvoni, wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

Do not stop taking Harvoni
Do not stop taking this medicine unless your doctor tells you to. It is very important that you complete the full course of treatment to give the medicine the best chance to treat your hepatitis C virus infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine may cause side effects. If you take Harvoni you may get one or more of the side effects below:

Very common side effects
(may affect more than 1 in 10 people)
- headache
- feeling tired

Common side effects
(may affect up to 1 in 10 people)
- rash

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Harvoni

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Harvoni contains

- **The active substances are** ledipasvir and sofosbuvir. Each film-coated tablet contains 90 mg ledipasvir and 400 mg sofosbuvir.

- **The other ingredients are**
  Tablet core:
  Copovidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate

  Film-coating:
  Polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, sunset yellow FCF aluminium lake (E110)

What Harvoni looks like and contents of the pack
The film-coated tablets are orange, diamond-shaped tablets debossed with "GSI" on one side and "7985" on the other side. The tablet is 19 mm long and 10 mm wide.

Each bottle contains a silica gel desiccant (drying agent) that must be kept in the bottle to help protect your tablets. The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The following pack sizes are available:

- outer cartons containing 1 bottle of 28 film-coated tablets
- outer cartons containing 3 bottles of 28 (84) film-coated tablets. Not all pack sizes may be marketed.

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Manufacturer
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IDA Business & Technology Park
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu