SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ledipasvir/Sofosbuvir Gilead® 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 157 mg of lactose (as monohydrate) and 47 micrograms of sunsetyellow FCF.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Ledipasvir/Sofosbuvir Gilead 90 mg/400 mg film-coated tablets
Orange, diamond-shaped, film-coated tablet of dimensions of approximately 19 mm x 10 mm, debossed with “GSI” on one side and “7985” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ledipasvir/Sofosbuvir Gilead is indicated for the treatment of chronic hepatitis C (CHC) in adult and paediatric patients aged 3 years and above (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

Ledipasvir/Sofosbuvir Gilead treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology

The recommended dose of Ledipasvir/Sofosbuvir Gilead in adults is 90 mg/400 mg once daily with or without food (see section 5.2).

The recommended dose of Ledipasvir/Sofosbuvir Gilead in paediatric patients aged 3 years and above is based on weight (as detailed in Table 2) and can be taken with or without food (see section 5.2).

A granule formulation of Ledipasvir/Sofosbuvir Gilead is available for the treatment of chronic HCV-infection in paediatric patients aged 3 years and above having difficulty swallowing film-coated tablets. Please refer to the Summary of Product Characteristics for Harvoni 33.75 mg/150 mg or 45 mg/200 mg granules.

Table 1: Recommended treatment duration for Ledipasvir/Sofosbuvir Gilead and the recommended use of co-administered ribavirin for certain subgroups

Patient population (including HIV co-infected patients)	**Treatment and duration**
Adult and paediatric patients aged 3 years and above[a] with genotype 1, 4, 5 or 6 CHC	
Patients without cirrhosis	Ledipasvir/Sofosbuvir Gilead for 12 weeks. - Ledipasvir/Sofosbuvir Gilead for 8 weeks may be considered in previously untreated genotype 1-infected patients (see section 5.1, ION-3 study).
Patients with compensated cirrhosis	Ledipasvir/Sofosbuvir Gilead + ribavirin[b,c] for 12 weeks or Ledipasvir/Sofosbuvir Gilead (without ribavirin) for 24 weeks. - Ledipasvir/Sofosbuvir Gilead (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	Ledipasvir/Sofosbuvir Gilead + ribavirin[b,c] for 12 weeks (see section 5.1). - Ledipasvir/Sofosbuvir Gilead (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	Ledipasvir/Sofosbuvir Gilead + ribavirin[d] for 12 weeks (see section 5.1) - Ledipasvir/Sofosbuvir Gilead (without ribavirin) for 24 weeks may be considered in patients who are ineligible for or intolerant to ribavirin.
Adult and paediatric patients 3 years of ageand above[a] with genotype 3 CHC	
Patients with compensated cirrhosis and/or prior treatment failure	Ledipasvir/Sofosbuvir Gilead + ribavirin[b] for 24 weeks (see sections 4.4 and 5.1).

a See Table 2 for weight-based Ledipasvir/Sofosbuvir Gilead dosing recommendations for paediatric patients aged 3 years and above.
b Adults: weight based ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg), administered orally in two divided doses
with food.
c Paediatric patients: for ribavirin dosing recommendations see table 4 below.
d For ribavirin dosing recommendations in adult patients with decompensated cirrhosis, see table 3 below.

Table 2: Dosing for paediatric patients aged 3 years and above using Ledipasvir/Sofosbuvir Gilead Tablets

Body Weight (kg)	**Dosing of Ledipasvir/Sofosbuvir Gilead Tablets**	**Ledipasvir/Sofosbuvir Daily Dose**
≥ 35	one 90 mg/400 mg tablet once daily or two 45 mg/200 mg tablets once daily	90 mg/400 mg/day
17 to < 35	one 45 mg/200 mg tablet once daily	45 mg/200 mg/day

* Ledipasvir/Sofosbuvir Gilead is also available as granules for use in paediatric patients with CHC aged 3 years and above (see section 5.1). Patients that weigh < 17 kg are not recommended to take tablets. Please refer to the Summary of Product Characteristics for Harvoni 33.75 mg/150 mg or 45 mg/200 mg granules.

Table 3: Guidance for ribavirin dosing when administered with Ledipasvir/Sofosbuvir Gilead to adult patients with decompensated cirrhosis

Patient	Ribavirin dose*
Child-Pugh-Turcotte (CPT) Class B cirrhosis pre-transplant	1,000 mg per day for patients < 75 kg and 1,200 mg for those weighing ≥ 75 kg
CPT Class C cirrhosis pre-transplant CPT Class B or C cirrhosis post-transplant	Starting dose of 600 mg, which can be titrated up to a maximum of 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg) if well tolerated. If the starting dose is not well tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels

* If a more normalized dose of ribavirin (by weight and renal function) cannot be reached for reasons of tolerability, 24 weeks of Ledipasvir/Sofosbuvir Gilead + ribavirin should be considered in order to minimize the risk for relapse.

For adults when ribavirin is added to Ledipasvir/Sofosbuvir Gilead, refer also to the Summary of Product Characteristics of ribavirin.

In paediatric patients aged 3 years and above the following ribavirin dosing is recommended where ribavirin is divided into two daily doses and given with food:

Table 4: Guidance for ribavirin dosing when administered with Ledipasvir/Sofosbuvir Gilead to paediatric patients aged 3 years and above.

Body weight kg	Ribavirin Dose*
< 47	15 mg/kg/day
47-49	600 mg/day
50-65	800 mg/day
66-74	1000 mg/day
> or = 75	1200 mg/day

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

Dose modification of ribavirin in adults taking 1,000-1,200 mg daily

If Ledipasvir/Sofosbuvir Gilead 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 5 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 5: Ribavirin dose modification guideline for co-administration with Ledipasvir/Sofosbuvir Gilead in adults

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).

Paediatric population aged < 3 years
The safety and efficacy of Ledipasvir/Sofosbuvir Gilead in paediatric patients aged < 3 years have not been established. No data are available.

Missed dose
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 Ledipasvir/Sofosbuvir Gilead is required for patients with mild or moderate renal impairment.

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) and end stage renal disease (ESRD) requiring dialysis. Ledipasvir/Sofosbuvir Gilead can be used in these patients with no dose adjustment when no other relevant treatment options are available (see section 4.4, 4.8, 5.1 and 5.2).

Hepatic impairment
No dose adjustment of Ledipasvir/Sofosbuvir Gilead 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).

Method of administration

For oral use.

Patients should be instructed to swallow the tablet(s) whole with or without food. Due to the bitter taste, it is recommended that film-coated tablets are 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 strong P-gp inducers

Medicinal products that are strong P-glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort). Co-administration will significantly decrease ledipasvir and sofosbuvir plasma concentrations and could result in loss of efficacy of Ledipasvir/Sofosbuvir Gilead (see section 4.5).

4.4 Special warnings and precautions for use

Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead in adults 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). In genotype 3-infection, the use of Ledipasvir/Sofosbuvir Gilead (always in combination with ribavirin) should only be considered for patients who are deemed at high risk for clinical disease progression and who do not have alternative treatment options.

The clinical data to support the use of Ledipasvir/Sofosbuvir Gilead in adults infected with HCV genotype 2 and 6 are limited (see section 5.1).

Severe bradycardia and heart block

Life-threatening cases of severe bradycardia and heart block have been observed when sofosbuvir- containing regimens are used in combination with amiodarone. Bradycardia has generally occurred within hours to days, but cases with a longer time to onset have been observed mostly up to 2 weeks after initiating HCV treatment.

Amiodarone should only be used in patients on Ledipasvir/Sofosbuvir Gilead 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 undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone, cardiac monitoring as outlined above should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Ledipasvir/Sofosbuvir Gilead.

All patients with concurrent or recent use of amiodarone should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

Use in diabetic patients

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

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.

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 classes of medicinal products for clearance of HCV infection. Consequently, consideration should be given to longer treatment for patients with uncertain subsequent retreatment options.

Renal impairment

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) and ESRD requiring haemodialysis. Ledipasvir/Sofosbuvir Gilead can be used in these patients with no dose adjustment when no other relevant treatment options are available (see sections 4.8, 5.1 and 5.2). When Ledipasvir/Sofosbuvir Gilead 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).

Adults 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 Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead.
Co-administration of such medicinal products is not recommended with Ledipasvir/Sofosbuvir Gilead (see section 4.5).

Use with certain HIV antiretroviral regimens

Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead 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).

Paediatric population

Ledipasvir/Sofosbuvir Gilead is not recommended for use in paediatric patients aged < 3 years because the safety and efficacy have not been established in this population.

Excipients

Ledipasvir/Sofosbuvir Gilead contains the azo colouring agent sunset yellow FCF (E110), which may cause allergic reactions. It also contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Potential for Ledipasvir/Sofosbuvir Gilead 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.

Potential for other medicinal products to affect Ledipasvir/Sofosbuvir Gilead

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

Medicinal products that are strong P-gp inducers (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort) may significantly decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of ledipasvir/sofosbuvir and thus are contraindicated with Ledipasvir/Sofosbuvir Gilead (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 Ledipasvir/Sofosbuvir Gilead. Co-administration with such medicinal products is not recommended with Ledipasvir/Sofosbuvir Gilead (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; Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead, a close monitoring of International Normalised Ratio (INR) values is recommended.

Impact of DAA therapy on drugs metabolized by the liver

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

Interactions between Ledipasvir/Sofosbuvir Gilead and other medicinal products

Table 6 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 6: Interactions between Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead**
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 Ledipasvir/Sofosbuvir Gilead administration by 4 hours.
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 Ledipasvir/Sofosbuvir Gilead[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 Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead [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		

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 Ledipasvir/Sofosbuvir Gilead**
Omeprazole (20 mg once daily)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c] Omeprazole dosed simultaneously with Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead. Proton pump inhibitors should not be taken before Ledipasvir/Sofosbuvir Gilead.
ANTIARRHYTHMICS		
Amiodarone	Effect on amiodarone, sofosbuvir and ledipasvir concentrations unknown.	Coadministration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia. Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with Ledipasvir/Sofosbuvir Gilead (see sections 4.4 and 4.8).
Digoxin	Interaction not studied. *Expected:* ↑ Digoxin ↔ Ledipasvir ↔ Sofosbuvir ↔ GS-331007 (Inhibition of P-gp)	Co-administration of Ledipasvir/Sofosbuvir Gilead with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with Ledipasvir/Sofosbuvir Gilead.
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 Ledipasvir/Sofosbuvir Gilead. 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 Ledipasvir/Sofosbuvir Gilead.
ANTICONVULSANTS		
Phenobarbital Phenytoin	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Ledipasvir/Sofosbuvir Gilead is contraindicated with phenobarbital and phenytoin (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 Ledipasvir/Sofosbuvir Gilead**
Carbamazepine	Interaction not studied *Expected:* ↓ Ledipasvir *Observed:* Sofosbuvir ↓ C_{max} 0.52 (0.43, 0.62) ↓ AUC 0.52 (0.46, 0.59) C_{min} (NA) GS-331007 ↔ C_{max} 1.04 (0.97, 1.11) ↔ AUC 0.99 (0.94, 1.04) C_{min} (NA) (Induction of P-gp)	Ledipasvir/Sofosbuvir Gilead is contraindicated with carbamazepine (see section 4.3).
Oxcarbazepine	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Ledipasvir/Sofosbuvir Gilead with oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir leading to reduced therapeutic effect of Ledipasvir/Sofosbuvir Gilead. 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)	Ledipasvir/Sofosbuvir Gilead is contraindicated with rifampicin (see section 4.3).
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)	

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 Ledipasvir/Sofosbuvir Gilead**
Rifabutin	Interaction not studied. *Expected:* ↓ Ledipasvir *Observed:* Sofosbuvir ↓ C_{max} 0.64 (0.53, 0.77) ↓ AUC 0.76 (0.63, 0.91) C_{min} (NA) GS-331007 ↔ C_{max} 1.15 (1.03, 1.27) ↔ AUC 1.03 (0.95, 1.12) C_{min} (NA) (Induction of P-gp)	Ledipasvir/Sofosbuvir Gilead is contraindicated with rifabutin (see section 4.3).
Rifapentine	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Ledipasvir/Sofosbuvir Gilead with rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Ledipasvir/Sofosbuvir Gilead. Such co-administration is not recommended.
SEDATIVES/HYPNOTICS		
Midazolam (2.5 mg single dose)/ ledipasvir (90 mg single dose) Ledipasvir (90 mg once daily)	*Observed:* Midazolam ↔ C_{max} 1.07 (1.00, 1.14) ↔ AUC 0.99 (0.95, 1.04) (Inhibition of CYP3A) Midazolam ↔ C_{max} 0.95 (0.87, 1.04) ↔ AUC 0.89 (0.84, 0.95) (Induction of CYP3A) *Expected:* ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Ledipasvir/Sofosbuvir Gilead or midazolam 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 Ledipasvir/Sofosbuvir Gilead**
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 Ledipasvir/Sofosbuvir Gilead or efavirenz/ emtricitabine/ 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 Ledipasvir/Sofosbuvir Gilead**
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 Ledipasvir/Sofosbuvir Gilead or emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate is required.
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 Ledipasvir/Sofosbuvir Gilead or abacavir/ lamivudine 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 Ledipasvir/Sofosbuvir Gilead
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 Ledipasvir/Sofosbuvir Gilead or atazanavir (ritonavir boosted) is required. For the combination of tenofovir/emtricitabine + atazanavir/ritonavir, please see below.
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, Ledipasvir/Sofosbuvir Gilead increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir/Sofosbuvir Gilead 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.

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 Ledipasvir/Sofosbuvir Gilead**
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 Ledipasvir/Sofosbuvir Gilead 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)	
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, Ledipasvir/Sofosbuvir Gilead increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir/Sofosbuvir Gilead 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).

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 Ledipasvir/Sofosbuvir Gilead
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, Ledipasvir/Sofosbuvir Gilead is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead with tipranavir (ritonavir boosted) is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect of Ledipasvir/Sofosbuvir Gilead. Co-administration is not recommended.
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 Ledipasvir/Sofosbuvir Gilead 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)	

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 Ledipasvir/Sofosbuvir Gilead
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, Ledipasvir/Sofosbuvir Gilead is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir/Sofosbuvir Gilead 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.
HERBAL SUPPLEMENTS		
St. John's wort	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Ledipasvir/Sofosbuvir Gilead is contraindicated with St. John's wort (see section 4.3).
HMG-CoA REDUCTASE INHIBITORS		
Rosuvastatin[g]	↑ Rosuvastatin (Inhibition of drug transporters OATP and BCRP)	Co-administration of Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead with rosuvastatin is contraindicated (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 Ledipasvir/Sofosbuvir Gilead**
Pravastatin[g]	↑ Pravastatin	Co-administration of Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead, 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 Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead or ciclosporin is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of ciclosporin may be required.
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 Ledipasvir/Sofosbuvir Gilead or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and

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 Ledipasvir/Sofosbuvir Gilead
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)	potential dose adjustment of tacrolimus may be required.
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 Ledipasvir/Sofosbuvir Gilead.
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 Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead 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 Ledipasvir/Sofosbuvir Gilead 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

Ledipasvir/Sofosbuvir Gilead 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, Ledipasvir/Sofosbuvir Gilead should not be used during breast-feeding.

Fertility

No human data on the effect of Ledipasvir/Sofosbuvir Gilead on fertility are available. Animal studies do not indicate harmful effects of ledipasvir or sofosbuvir on fertility.

If ribavirin is co-administered with Ledipasvir/Sofosbuvir Gilead, 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

Ledipasvir/Sofosbuvir Gilead (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 in adults

The safety assessment of Ledipasvir/Sofosbuvir Gilead was mainly based on pooled Phase 3 clinical studies, without a control, in 1952 patients who received Ledipasvir/Sofosbuvir Gilead for 8, 12 or 24 weeks, including 872 patients who received Ledipasvir/Sofosbuvir Gilead in combination with ribavirin.

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.

Tabulated list of adverse events

The following adverse drug reactions have been identified with Ledipasvir/Sofosbuvir Gilead (Table 7). 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 7: Adverse drug reactions identified with Ledipasvir/Sofosbuvir Gilead

Frequency	Adverse drug reaction
Nervous system disorders:	
Very common	headache
Skin and subcutaneous tissue disorders:	
Common	rash
Not known	angioedema
General disorders:	
Very common	fatigue

Adults 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 adults with decompensated liver disease and/or those post-liver transplant was assessed in two open-label studies (SOLAR-1 and SOLAR-2). 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 15% of the patients.

7% of liver transplant recipients had a modification of their

immunosuppressive agents. Patients with renal impairment

Ledipasvir/sofosbuvir was administered for 12 weeks to 18 patients with genotype 1 CHC and severe renal impairment in an open-label study (Study 0154). In this limited clinical safety data set, the rate of adverse events was not clearly elevated from what is expected in patients with severe renal impairment.

The safety of Ledipasvir/Sofosbuvir Gilead has been evaluated in a 12-week non-controlled study including 95 patients with ESRD requiring dialysis (Study 4063). In this setting, exposure of sofosbuvir metabolite GS- 331007 is 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients.

Paediatric population

The safety and efficacy of Ledipasvir/Sofosbuvir Gilead in paediatric patients aged 3 years and above are based on data from a Phase 2, open-label clinical study (Study 1116) that enrolled 226 patients who were treated with ledipasvir/sofosbuvir for 12 or 24 weeks or ledipasvir/sofosbuvir plus ribavirin for 24 weeks. The adverse reactions observed were consistent with those observed in clinical studies of ledipasvir/sofosbuvir in adults (see Table 7).

Description of selected adverse reactions

Cardiac arrhythmias
Cases of severe bradycardia and heart block have been observed when Ledipasvir/Sofosbuvir Gilead is used with amiodarone and/or other drugs that lower heart rate (see sections 4.4 and 4.5).

Skin disorders
Frequency not known: Stevens-Johnson syndrome

Reporting of suspected adverse reactions

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 Ledipasvir/Sofosbuvir Gilead. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Ledipasvir/Sofosbuvir Gilead 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: J05AP51 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 8. 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 8: 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 – Adults-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).

Among post-transplant patients with compensated liver disease or patients with decompensated liver disease either pre- or post-transplant (SOLAR-1 and SOLAR-2 studies), relapse was associated with the detection of one or more of the following NS5A RAVs: K24R, M28T, Q30R/H/K, L31V, H58D and Y93H/C in 12/14 genotype 1a patients, and L31M, Y93H/N in 6/6 genotype 1b patients.

A NS5B substitution E237G was detected in 3 patients (1 genotype 1b and 2 genotype 1a) in the Phase 3 studies (ION-3, ION-1 and ION-2) and 3 patients with genotype 1a infection in the SOLAR-1 and SOLAR-2 studies at the time of relapse. The E237G substitution showed a 1.3-fold reduction in susceptibility to sofosbuvir in the genotype 1a replicon assay. The clinical significance of this substitution is currently unknown.

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 clinical studies – Adults-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. In the SOLAR-2 study, one patient with genotype 4d developed NS5B substitution E237G at the time of relapse. The clinical significance of this substitution is currently unknown.

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.

<u>Effect of baseline HCV resistance-associated variants on treatment outcome</u>

Adults-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.

Among post-transplant patients with compensated liver disease (SOLAR-1 and SOLAR-2 studies), no relapse occurred in patients with baseline NS5A RAVs (n = 23) following 12 weeks of treatment with ledipasvir/sofosbuvir + ribavirin. Among patients with decompensated liver disease (pre- and post- transplant), 4/16 (25%) patients with NS5A RAVs conferring > 100-fold resistance relapsed after
12 weeks treatment with ledipasvir/sofosbuvir + ribavirin compared to 7/120 (6%) in those without
any baseline NS5A RAVs or RAVs conferring a fold-change of ≤ 100.

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.

Adults-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.

Paediatric Patients

The presence of pre-treatment NS5A and/or NS5B RAVs did not impact treatment outcome as all subjects with pre-treatment RAVs achieved SVR12 and SVR24. One 8-year-old subject infected with genotype 1a HCV who failed to achieve SVR12 had no NS5A or NS5B nucleoside inhibitor RAVs at baseline and had emergent NS5A RAV Y93H at relapse.

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 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 9: 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 10: 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 11: 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 12: 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 13: 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 14: 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 15: 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 16 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 16: 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 17: 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 and SOLAR-2
SOLAR-1 and SOLAR-2 were two open-label clinical studies that evaluated 12 and 24 weeks of treatment with ledipasvir/sofosbuvir in combination with ribavirin in genotype 1 and 4 HCV-infected patients who have undergone liver transplantation and/or who have decompensated liver disease. The two studies were identical in study design. Patients were enrolled in one of the seven groups based on liver transplantation status and severity of hepatic impairment (see Table 18). Patients with a CPT score > 12 were excluded. Within each group, patients were randomized in a 1:1 ratio to receive ledipasvir/sofosbuvir + ribavirin for 12 or 24 weeks.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 670 treated patients, the median age was 59 years (range: 21 to 81 years); 77% of the patients were male; 91% were White; mean body mass index was 28 kg/m^2 (range: 18 to 49 kg/m^2); 94% and 6% had genotype 1 and 4 HCV infection, respectively; 78% of the patients failed a prior HCV therapy. Among the patients who had decompensated cirrhosis (pre- or post-transplant), 64% and 36% were CPT class B and C at screening, respectively, 24% had a baseline Model for End Stage Liver Disease (MELD) score greater than 15.

Table 18: Combined response rates (SVR12) in studies SOLAR-1 and SOLAR-2

	LDV/SOF+RBV 12 weeks (n = 307)[a,b]	**LDV/SOF+RBV 24 weeks (n = 307)[a,b]**
	SVR	**SVR**
Pre-transplant		
CPT B	87% (45/52)	92% (46/50)
CPT C	88% (35/40)	83% (38/46)
Post-transplant		
Metavir score F0-F3	95% (94/99)	99% (99/100)
CPT A[c]	98% (55/56)	96% (51/53)
CPT B[c]	89% (41/46)	96% (43/45)
CPT C[c]	57% (4/7)	78% (7/9)
FCH	100% (7/7)	100% (4/4)

a Twelve patients transplanted prior to post-treatment Week 12 with HCV RNA< LLOQ at last measurement prior to transplant were excluded.

b Two patients who did not have decompensated cirrhosis and had also not received a liver transplant were excluded due to failure to meet the inclusion criteria for any of the treatment groups.

c CPT = Child-Pugh-Turcotte, FCH = Fibrosing cholestatic hepatitis. CPT A = CPT score 5-6 (compensated), CPT B = CPT score 7-9 (decompensated), CPT C = CPT score 10-12 (decompensated).

Forty patients with genotype 4 CHC were enrolled in SOLAR-1 and SOLAR-2 studies, SVR12 were 92% (11/12) and 100% (10/10) in post-transplant patients without decompensated cirrhosis and 60% (6/10) and 75% (6/8) in patients with decompensated cirrhosis (pre- and post-liver transplantation) treated for 12 or 24 weeks, respectively. Of the 7 patients who failed to achieve SVR12, 3 relapsed, all had decompensated cirrhosis and were treated with ledipasvir/sofosbuvir + ribavirin for 12 weeks.

Changes in MELD and CPT score from baseline to post-treatment Week 12 were analyzed for all patients with decompensated cirrhosis (pre- or post-transplant) who achieved SVR12 and for whom data were available (n = 123) to assess the effect of SVR12 on hepatic function.

Change in MELD score: Among those who achieved SVR12 with 12 weeks treatment with ledipasvir/sofosbuvir + ribavirin, 57% (70/123) and 19% (23/123) had an improvement or no change in MELD score from baseline to post-treatment week 12, respectively; of the 32 patients whose MELD score was ≥ 15 at baseline, 59% (19/32) 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 score and class: Among those who achieved SVR12 with 12 weeks treatment with ledipasvir/sofosbuvir with ribavirin, 60% (74/123) and 34% (42/123) had an improvement or no change of CPT scores from baseline to post-treatment week 12, respectively; of the 32 patients who had CPT C cirrhosis at baseline, 53% (17/32) had CPT B cirrhosis at post-treatment Week 12; of the 88 patients who had CPT B cirrhosis at baseline, 25% (22/88) 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 19). For genotype 3 infection, ledipasvir/sofosbuvir was given with or without ribavirin, also for 12 weeks (Table 20).

Table 19: 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 20: 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.

Patients with renal impairment

Study 0154 was an open-label clinical study that evaluated the safety and efficacy of 12 weeks of treatment with ledipasvir/sofosbuvir in 18 genotype 1 HCV-infected patients with severe renal impairment not requiring dialysis. At baseline, two patients had cirrhosis and the mean eGFR was 24.9 mL/min (range: 9.0-39.6). SVR12 was achieved in 18/18 patients.

Study 4063 was an open-label three-arm clinical study that evaluated 8, 12, and 24 weeks of treatment with ledipasvir/sofosbuvir in a total of 95 patients with genotype 1 (72%), 2 (22%), 4 (2%), 5 (1%), or 6 (2%) CHC and ESRD requiring dialysis: 45 treatment-naïve genotype 1 HCV-infected patients without cirrhosis received ledipasvir/sofosbuvir for 8 weeks; 31 treatment-experienced genotype 1 HCV-infected patients and treatment-naïve or treatment-experienced patients with genotype 2, 5, and 6 infection without cirrhosis received ledipasvir/sofosbuvir for 12 weeks; and 19 genotype 1, 2, and 4 HCV-infected patients with compensated cirrhosis received ledipasvir/sofosbuvir for 24 weeks. Of the 95 total patients, at baseline, 20% of patients had cirrhosis, 22% were treatment experienced, 21% had received a kidney transplant, 92% were on hemodialysis, and 8% were on peritoneal dialysis; mean duration on dialysis was 11.5 years (range: 0.2 to 43.0 years). The SVR rates for the 8, 12, and 24 week ledipasvir/sofosbuvir treatment groups were 93% (42/45), 100% (31/31), and 79% (15/19), respectively. Of the seven patients who did not achieve SVR12, none experienced virologic failure or relapsed.

Paediatric population

The efficacy of ledipasvir/sofosbuvir in HCV infected patients aged 3 years and above was evaluated in a Phase 2, open label clinical study that enrolled 226 patients: 221 patients with genotype 1, 2 patients with genotype 3, and 3 patients with genotype 4 CHC (Study 1116) (see section 4.2 for information on paediatric use).

Patients aged 12 to < 18 Years:

Ledipasvir/sofosbuvir was evaluated in 100 patients aged 12 to < 18 years with genotype 1 HCV infection. A total of 80 patients (n=80) were treatment-naïve, while 20 patients (n=20) were treatment-experienced. All patients were treated with ledipasvir/sofosbuvir for 12 weeks.

Demographics and baseline characteristics were balanced across treatment-naïve and treatment-experienced patients. The median age was 15 years (range: 12 to 17); 63% of the patients were female; 91% were White, 7% were Black, and 2% were Asian; 13% were Hispanic/Latino; mean weight was 61.3 kg (range: 33.0 to 126.0 kg); 55% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 81% had genotype 1a HCV infection; and 1 patient who was treatment naïve was known to have cirrhosis. The majority of patients (84%) had been infected through vertical transmission.

The SVR12 rate was 98% overall (98% [78/80] in treatment-naïve patients and 100% [20/20] in treatment experienced patients). A total of 2 out of 100 patients (2%), both treatment- naïve, did not achieve SVR12 (due to loss to follow-up). No patient experienced virologic failure.

Patients aged 6 to < 12 Years:
Ledipasvir/sofosbuvir was evaluated in 92 patients aged 6 to < 12 years with genotype 1, 3, or 4 HCV-infection. A total of 72 patients (78%) were treatment-naïve and 20 patients (22%) were treatment-experienced. Eighty-nine of the patients (87 patients with genotype 1 HCV infection and 2 patients with genotype 4 HCV infection) were treated with ledipasvir/sofosbuvir for 12 weeks, 1 treatment experienced patient with genotype 1 HCV infection and cirrhosis was treated with ledipasvir/sofosbuvir for 24 weeks, and 2 treatment experienced patients with genotype 3 HCV infection were treated with ledipasvir/sofosbuvir plus ribavirin for 24 weeks.

The median age was 9 years (range: 6 to 11); 59% of the patients were male; 79% were White, 8% were Black, and 5% were Asian; 10% were Hispanic/Latino; mean weight was 32.8 kg (range: 17.5 to
76.4 kg); 59% had baseline HCV RNA levels greater than or equal to 800,000 IU/ mL; 84% had genotype 1a HCV infection; 2 patients (1 treatment-naïve, 1 treatment-experienced) had known cirrhosis. The majority of patients (97%) had been infected through vertical transmission.

The SVR rate was 99% overall (99% [88/89], 100% [1/1], and 100% [2/2] in patients treated with ledipasvir/sofosbuvir for 12 weeks, ledipasvir/sofosbuvir for 24 weeks, and ledipasvir/sofosbuvir plus ribavirin for 24 weeks, respectively). The one treatment-naïve patient with genotype 1 HCV infection and cirrhosis who was treated with Ledipasvir/Sofosbuvir Gilead for 12 weeks did not achieve SVR12 and relapsed.

Patients aged 3 to < 6 Years:
Ledipasvir/sofosbuvir was evaluated in 34 patients aged 3 to < 6 years with genotype 1 (n = 33) or genotype 4 (n = 1) HCV-infection. All of the patients were treatment-naïve and treated with ledipasvir/sofosbuvir for 12 weeks. The median age was 5 years (range: 3 to 5); 71% of the patients were female; 79% were White, 3% were Black, and 6% were Asian; 18% were Hispanic/Latino; mean weight was 19.2 kg (range: 10.7 to 33.6 kg); 56% had baseline HCV RNA levels greater than or equal to 800,000 IU/ mL; 82% had genotype 1a HCV infection; no patients had known cirrhosis. All patients (100%) had been infected through vertical transmission.

The SVR rate was 97% overall (97% [32/33] in patients with genotype 1 HCV

infection and 100% [1/1] in patients with genotype 4 HCV infection). One patient who prematurely discontinued study treatment after five days due to abnormal taste of the medication did not achieve SVR.

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. Ledipasvir/Sofosbuvir Gilead 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
A summary of the effect of varying degrees of renal impairment (RI) on the exposures of the components of Ledipasvir/Sofosbuvir Gilead compared to subjects with normal renal function, as described in the text below, are provided in Table 21.

Table 21: Effect of Varying Degrees of Renal Impairment on Exposures (AUC) of Sofosbuvir, GS-331007, and Ledipasvir Compared to Subjects with Normal Renal Function

	HCV-Negative Subjects					HCV-Infected Subjects	
	Mild RI (eGFR ≥50 and <80 mL/ min/ 1.73m^2)	Moderate RI (eGFR ≥30 and <50 mL/ min/ 1.73m^2)	Severe RI (eGFR <30 mL/ min/ 1.73m^2)	ESRD Requiring Dialysis		Severe RI (eGFR <30 mL/ min/ 1.73m^2)	ESRD Requiring Dialysis
				Dosed 1 hr Before Dialysis	Dosed 1 hr After Dialysis		
Sofosbuvir	1.6-fold↑	2.1-fold↑	2.7-fold↑	1.3-fold↑	1.6-fold↑	~2-fold↑	1.9-fold↑
GS-331007	1.6-fold↑	1.9-fold↑	5.5-fold↑	≥10-fold↑	≥20-fold↑	~6-fold↑	23-fold↑
Ledipasvir	-	-	↔	-	-	-	1.6-fold↑

↔ indicates no clinically relevant change in the exposure of Ledipasvir.

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative adult patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault, median [range] CrCl 22 [17-29] mL/min).

The pharmacokinetics of sofosbuvir were studied in HCV negative adult 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). 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.

In HCV-infected adult patients with severe renal impairment treated with ledipasvir/sofosbuvir for 12 weeks (n = 18), the pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 were consistent with that observed in HCV negative patients with severe renal impairment.

The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 were studied in HCV-infected adult patients with ESRD requiring dialysis treated with ledipasvir/sofosbuvir (n=94) for 8, 12, or 24 weeks, and compared to patients without renal impairment in the ledipasvir/sofosbuvir Phase 2/3 trials.

Hepatic impairment
The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative adult 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 adult patients indicated that cirrhosis (including decompensated 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 adult 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 (including decompensated 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
Ledipasvir, sofosbuvir, and GS-331007 exposures in paediatric patients aged 3 years and above were similar to those in adults from Phase 2/3 studies, following administration of ledipasvir/sofosbuvir. The 90% confidence intervals of geometric least-squares mean ratios for all PK parameters of interest were contained within the predetermined similarity bounds of less than 2-fold (50% to 200%) with the exception of ledipasvir C_{tau} in paediatric patients 12 years and above which was 84% higher (90%CI: 168% to 203%) and was not considered clinically relevant.

The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 have not been established in paediatric patients aged < 3 years (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 26-week rasH2 transgenic mouse and the 2-year rat carcinogenicity studies at exposures up to 26-times in mice and 8-times in rats higher than human exposure.

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.

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that ledipasvir has the potential to be very persistent and very bioaccumulative (vPvB) in the environment (see section 6.6).

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 partially hydrolyzed
Titanium dioxide
Macrogol
Talc
Sunset yellow FCF (E110) (Ledipasvir/Sofosbuvir Gilead 90 mg/400 mg film-coated tablet only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

6 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Ledipasvir/Sofosbuvir Gilead 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 for the 90 mg/400 mg tablets only; 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.

This medicinal product may pose a risk to the environment (see section 5.3).

7 MARKETING AUTHORISATION HOLDER

Gilead Sciences Ltd
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London
WC1V 7EE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 11972/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

09/06/2025