MyHep LVIR®
75080656

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For the use of a Hepatologist only

℞ Ledipasvir and Sofosbuvir Tablets 90 mg+400 mg

MyHep LVIR®

1. GENERIC NAME

Ledipasvir and Sofosbuvir 90 mg + 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablets contains:

Ledipasvir	90 mg
Sofosbuvir	400 mg

For the full list of excipients, see section 6 in the Patient Counselling Information.

3. DOSAGE FORMS AND STRENGTH

Ledipasvir and Sofosbuvir 90 mg + 400 mg film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets are indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults (see sections 4.2, 4.4 and 5.2).

4.2 Posology and method of administration

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology

The recommended dose of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets is one tablet once daily with or without food (see section 5.3).

Table 1: Recommended treatment duration for Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets and the recommended use of co-administered ribavirin for certain subgroups

Patient population (including HIV co-infected patients)	**Treatment and duration**
Patients with genotype 1 CHC	
Patients without cirrhosis	Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets for 12 weeks. - Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets for 8 weeks may be considered in previously untreated genotype 1-infected patients (see section 5.2, ION-3 study).
Patients with compensated cirrhosis	Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets + ribavirin [a] for 12 weeks or Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets (without ribavirin) for 24 weeks. - Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets (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 90 mg/400 mg film coated tablets + ribavirin [a] for 12 weeks (see section 5.2). - Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets (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 90 mg/400 mg film coated tablets+ ribavirin[b] for 12 weeks (see section 5.2). - Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets (without ribavirin) for 24 weeks may be considered in patients who are ineligible for or intolerant to ribavirin.

a Ribavirin dose: weight-based ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg), administered orally in two divided doses with food.

b For ribavirin dosing recommendations in patients with decompensated cirrhosis, see table 2 below.

Table 2: Guidance for ribavirin dosing when administered with Ledipasvir/Sofosbuvir 90 mg/ 400 mg film coated tablets to 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 posttransplant	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 90 mg/400 mg film coated tablets + ribavirin should be considered in order to minimize the risk for relapse.

When ribavirin is added to Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets, refer also to the Summary of Product Characteristics of ribavirin.

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

If Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 in severity. Table 3 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 3: Ribavirin dose modification guideline for co-administration with Ledipasvir/ Sofosbuvir 90 mg/400 mg film coated tablets 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

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets are not recommended in children and adolescents aged less than 18 years of age.

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 5.3).

Renal impairment

No dose adjustment of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets is required for patients with mild or moderate renal impairment.

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) and end stage renal disease (ESRD) requiring dialysis. Ledipasvir/ Sofosbuvir 90 mg/400 mg film coated tablets can be used in these patients with no dose adjustment when no other relevant treatment options are available (see section 4.4, 4.8, 5.2 and 5.3)

Hepatic impairment

No dose adjustment of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C) (see section 5.3). Safety and efficacy of ledipasvir/sofosbuvir have been established in patients with decompensated cirrhosis (see section 5.2).

Method of administration

For oral use.

Patients should be instructed to swallow the tablet whole with or without food. Due to the bitter taste, it is recommended that the film-coated tablets are not chewed or crushed (see section 5.3).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients.
- Co-administration with rosuvastatin (see section 4.5).
- Use with potent P-gp inducers

Medicinal products that are potent P-glycoprotein (P-gp) inducers in the intestine (rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin). Co-administration will significantly decrease ledipasvir and sofosbuvir plasma concentrations and could result in loss of efficacy of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets (see section 4.5).

4.4 Special warnings and precautions for use

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets should not be administered concomitantly with other medicinal products containing sofosbuvir.

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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets.

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

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 m²) and ESRD requiring haemodialysis. Ledipasvir/Sofosbuvir 90 mg/ 400 mg film coated tablets 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 90 mg/400 mg film coated tablets 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 5.3).

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 90 mg/ 400 mg film coated tablets 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 90 mg/ 400 mg film coated tablets. Co-administration of such medicinal products is not recommended with Ledipasvir/Sofosbuvir 90 mg/ 400 mg film coated tablets (see section 4.5).

Use with certain HIV antiretroviral regimens

Ledipasvir/Sofosbuvir 90 mg/ 400 mg film coated tablets 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 90 mg/ 400 mg film coated tablets and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/ 400 mg film coated tablets 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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets are not recommended in children and adolescents aged less than 18 years.

Excipients

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets contains Opadry blue which may cause allergic reactions. It also contains lactose. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

As Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets contains ledipasvir and sofosbuvir, any

interactions that have been identified with these active substances individually may occur with Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets.

Potential for Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets

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 90 mg/400 mg film coated tablets (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 90 mg/400 mg film coated tablets. Co-administration with such medicinal products is not recommended with Ledipasvir/Sofosbuvir 90 mg /400 mg film coated tablets (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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets, 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 90 mg/400 mg film coated tablets and other medicinal products

Table 4 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 4: Interactions between Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets and other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels.** **Mean ratio (90% confidence interval) for AUC, Cmax, Cmin** [a, b]	**Recommendation concerning co-administration with Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets**
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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets [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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets [d]	Ledipasvir ↓ C_{max} 0.83 (0.69, 1.00) ↔ AUC 0.98 (0.80, 1.20) Sofosbuvir ↔ C_{max} 1.00 (0.76, 1.32) ↔ AUC 0.95 (0.82, 1.10) GS-331007 ↔ C_{max} 1.13 (1.07, 1.20) ↔ AUC 1.06 (1.01, 1.12) (Increase in gastric pH)	
Proton pump inhibitors		
Omeprazole (20 mg once daily)/ ledipasvir (90 mg single dose) c/ sofosbuvir (400 mg single dose) [c] Omeprazole dosed simultaneously with Ledipasvir / Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets. Proton pump inhibitors should not be taken before Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablet.
ANTIARRHYTHMICS		
Amiodarone	Effect on amiodarone and 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 90 mg/400 mg film coated tablets (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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets.
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 90 mg/400 mg film coated tablets. 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 90 mg/400 mg film coated tablets.
ANTICONVULSANTS		
Phenobarbital Phenytoin	Interaction not studied. *Expected*: ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets are contraindicated with phenobarbital and phenytoin (see section 4.3).
Oxcarbazepine	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets with oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir leading to reduced therapeutic effect of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets. Such co-administration is not recommended (see section 4.4).
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 90 mg/400 mg film coated tablets are contraindicated with carbamazepine (see section 4.3).
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 90 mg/400 mg film coated tablets 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)	
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 (0.9, 1.12) C_{min} (NA) (Induction of P-gp)	Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets with rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets. 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 90 mg/400 mg film coated tablets or midazolam is required.
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 90 mg/400 mg film coated tablets or efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is required.
Emtricitabine/rilpivirine /tenofovir disoproxil fumarate (200 mg/ 25 mg/ 300 mg once daily) /ledipasvir (90 mg once daily) c/ sofosbuvir (400 mg once daily)[c, d]	Emtricitabine ↔ C_{max} 1.02 (0.98, 1.06) ↔ AUC 1.05 (1.02, 1.08) ↔ C_{min} 1.06 (0.97, 1.15) Rilpivirine ↔ C_{max} 0.97 (0.88, 1.07) ↔ AUC 1.02 (0.94, 1.11) ↔ C_{min} 1.12 (1.03, 1.21) Tenofovir ↔ C_{max} 1.32 (1.25, 1.39) ↑ AUC 1.40 (1.31, 1.50) ↑ C_{min} 1.91 (1.74, 2.10) Ledipasvir ↔ C_{max} 1.01 (0.95, 1.07) ↔ AUC 1.08 (1.02, 1.15) ↔ C_{min} 1.16 (1.08, 1.25) Sofosbuvir ↔ C_{max} 1.05 (0.93, 1.20) ↔ AUC 1.10 (1.01, 1.21) GS-331007 ↔ C_{max} 1.06 (1.01, 1.11) ↔ AUC 1.15 (1.11, 1.19) ↔ C_{min} 1.18 (1.13, 1.24)	No dose adjustment of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets or abacavir/ lamivudine is required.
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Atazanavir boosted with ritonavir (300 mg/ 100 mg once daily)/ ledipasvir (90 mg once daily) c/ sofosbuvir (400 mg once daily) [c, d]	Atazanavir ↔ C_{max} 1.07 (1.00, 1.15) ↔ AUC 1.33 (1.25, 1.42) ↑ C_{min} 1.75 (1.58, 1.93) Ledipasvir ↑ C_{max} 1.98 (1.78, 2.20) ↑ AUC 2.13 (1.89, 2.40) ↑ C_{min} 2.36 (2.08, 2.67) Sofosbuvir ↔ C_{max} 0.96 (0.88, 1.05) ↔ AUC 1.08 (1.02, 1.15) GS-331007 ↔ C_{max} 1.13 (1.08, 1.19) ↔ AUC 1.23 (1.18, 1.29) ↔ C_{min} 1.28 (1.21, 1.36)	No dose adjustment of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir /Sofosbuvir 90 mg/400 mg film coated tablets and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4). Atazanavir concentrations are also increased, with a risk for an increase in bilirubin levels/icterus. That risk is even higher if ribavirin is used as part of the HCV treatment.
Darunavir boosted with ritonavir (800 mg/ 100 mg once daily)/ ledipasvir (90 mg once daily) [d]	Darunavir ↔ C_{max} 1.02 (0.88, 1.19) ↔ AUC 0.96 (0.84, 1.11) ↔ C_{min} 0.97 (0.86, 1.10) Ledipasvir ↑ C_{max} 1.45 (1.34, 1.56) ↑ AUC 1.39 (1.28, 1.49) ↑ C_{min} 1.39 (1.29, 1.51)	No dose adjustment of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Lopinavir boosted with ritonavir + emtricitabine/ tenofovir disoproxil fumarate	Interaction not studied. Expected: ↑ Lopinavir ↑ Ritonavir ↔ Emtricitabine ↑ Tenofovir ↑ Ledipasvir ↔ Sofosbuvir ↔ GS-331007	When given with lopinavir/ritonavir used in conjunction with tenofovir disoproxil fumarate, Ledipasvir / Sofosbuvir 90 mg/400 mg film coated tablets is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not 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 90 mg/400 mg film coated tablets with tipranavir (ritonavir boosted) is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets. 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 90 mg/400 mg film coated tablets or raltegravir is required.
Raltegravir (400 mg twice daily)/ sofosbuvir (400 mg once daily) [d]	Raltegravir ↓ C_{max} 0.57 (0.44, 0.75) ↓ AUC 0.73 (0.59, 0.91) ↔ C_{min} 0.95 (0.81, 1.12) Sofosbuvir ↔ C_{max} 0.87 (0.71, 1.08) ↔ AUC 0.95 (0.82, 1.09) GS-331007 ↔ C_{max} 1.09 (0.99, 1.19) ↔ AUC 1.02 (0.97, 1.08)	
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (150 mg/ 150 mg/ 200 mg/ 300 mg once daily) / ledipasvir (90 mg once daily) c/ sofosbuvir (400 mg once daily) [c]	Interaction not studied. *Expected:* ↔ Emtricitabine ↑ Tenofovir *Observed:* Elvitegravir ↔ C_{max} 0.88 (0.82, 0.95) ↔ AUC 1.02 (0.95, 1.09) ↑ C_{min} 1.36 (1.23, 1.49) Cobicistat ↔ C_{max} 1.25 (1.18, 1.32) ↑ AUC 1.59 (1.49, 1.70) ↑ C_{min} 4.25 (3.47, 5.22) Ledipasvir ↑ C_{max} 1.63 (1.51, 1.75) ↑ AUC 1.78 (1.64, 1.94) ↑ C_{min} 1.91 (1.76, 2.08) Sofosbuvir ↑ C_{max} 1.33 (1.14, 1.56) ↑ AUC 1.36 (1.21, 1.52) GS-331007 ↑ C_{max} 1.33 (1.22, 1.44) ↑ AUC 1.44 (1.41, 1.48) ↑ C_{min} 1.53 (1.47, 1.59)	When given with elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate, Ledipasvir/ Sofosbuvir 90 mg/400 mg film coated tablets is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets 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 90 mg/ 400 mg film coated tablets with rosuvastatin is contraindicated (see section 4.3).
Pravastatin [g]	↑ Pravastatin	Co-administration of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/ 400 mg film coated tablets, 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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets or tacrolimus is required at initiation of co-administration. Afterwards, close monitoring and potential dose adjustment of tacrolimus may be required.
Tacrolimus (5 mg single dose)/ sofosbuvir (400 mg single dose) [h]	Tacrolimus ↓ C_{max} 0.73 (0.59, 0.90) ↑ AUC 1.09 (0.84, 1.40) Sofosbuvir ↓ C_{max} 0.97 (0.65, 1.43) ↑ AUC 1.13 (0.81, 1.57) GS-331007 ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13)	
ORAL CONTRACEPTIVES		
Norgestimate / ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ ledipasvir (90 mg once daily)[d]	Norelgestromin ↔ C_{max} 1.02 (0.89, 1.16) ↔ AUC 1.03 (0.90, 1.18) ↔ C_{min} 1.09 (0.91, 1.31) Norgestrel ↔ C_{max} 1.03 (0.87, 1.23) ↔ AUC 0.99 (0.82, 1.20) ↔ C_{min} 1.00 (0.81, 1.23) Ethinyl estradiol ↑ C_{max} 1.40 (1.18, 1.66) ↔ AUC 1.20 (1.04, 1.39) ↔ C_{min} 0.98 (0.79, 1.22)	No dose adjustment of oral contraceptives is required.
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily)[d]	Norelgestromin ↔ C_{max} 1.07 (0.94, 1.22) ↔ AUC 1.06 (0.92, 1.21) ↔ C_{min} 1.07 (0.89, 1.28) Norgestrel ↔ C_{max} 1.18 (0.99, 1.41) ↑ AUC 1.19 (0.98, 1.45) ↑ C_{min} 1.23 (1.00, 1.51) Ethinyl estradiol ↔ C_{max} 1.15 (0.97, 1.36) ↔ AUC 1.09 (0.94, 1.26) ↔ C_{min} 0.99 (0.80, 1.23)	

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00.

b. All interaction studies conducted in healthy volunteers.

c. Administered as Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets.

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 90 mg/400 mg film coated tablets 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 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy and lactation

Women of childbearing potential / contraception in males and females

When Ledipasvir/ Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets 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 90 mg /400 mg film coated tablets 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 90 mg/400 mg film coated tablets should not be used during breast-feeding.

Fertility

No human data on the effect of Ledipasvir/ Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets, the contraindications regarding use of ribavirin during pregnancy and breast-feeding apply (see also the Summary of Product Characteristics for ribavirin).

Paediatric Population

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets are not recommended in children and adolescents aged less than 18 years of age.

Elderly

No dose adjustment is warranted for elderly patients (see section 5.3).

Renal impairment

No dose adjustment of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets is required for patients with mild or moderate renal impairment.

Safety data are limited in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) and end stage renal disease (ESRD) requiring dialysis. Ledipasvir/ Sofosbuvir 90 mg/400 mg film coated tablets can be used in these patients with no dose adjustment when no other relevant treatment options are available (see section 4.4, 4.8, 5.2 and 5.3)

Hepatic impairment

No dose adjustment of Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C) (see section 5.3). Safety and efficacy of ledipasvir/sofosbuvir have been established in patients with decompensated cirrhosis (see section 5.2).

4.7 Effects on ability to drive and use machines

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets (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 90 mg/400 mg film coated tablets was mainly based on pooled Phase 3 clinical studies, without a control, in 1952 patients who received Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets for 8, 12 or 24 weeks, including 872 patients who received Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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 90 mg/400 mg film coated tablets (Table 5). 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 5: Adverse drug reactions identified with Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets

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 5.2 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 90 mg/400 mg film coated tablets 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 GS331007 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

Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets are not recommended in children and adolescents aged less than 18 years of age.

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets 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

Mylan Laboratories Limited Packaging Development	**Artwork Implementation Schedule** **Check (✓) whichever is applicable** **(Approval is not valid without following details)**	**Date of Issue**		**Issued By**	
		Date of Return			
		Material Code	75080656	**Supersedes** 75068906	**Market** MYLAN-INDIA
[ ] New Component [ ] Immediately (Stock of superseded component to be destroyed, if applicable.) [ ] After consumption of existing (superseded) stock. [ ] Other (Specify)		**Description**	LIT. MYHEP LVIR TABS 90 mg/400 mg MYLAN-INDIA V3		
		Component	Printed Literature	**Actual Size**	Flat- 400 x 680 mm; Folded- 35 x 51 mm
		Substrate	40gsm ITC Tribeni Paper		
		Design & Style	Supply in Folded form as Proposed Size (with tape)		
Sign. dd/mm/yy Job Function / Sign. dd/mm/yy Job Function / Sign. dd/mm/yy Job Function		**Reason for Issue**	Change in Text and Size		

Printing Pantone Nos								
	1	BLACK	2	NA	3	NA	4	NA
	5	NA	6	NA	7	NA	8	NA
Non Printing	●	Die Line	○	NA	○	NA	○	NA

Proof No.	1	2	3	4	5
Date	30.07.2021	17.08.2021	dd/mm/yy	dd/mm/yy	dd/mm/yy
Remarks	Revised a/w.	Corrections 03.08	x	x	x
SOP-000565164-FORM-000565208-A01-03-01-20		**Final Date**	dd-mm-yy		

Prepared By	**Checked By**		**Approved By**	
Packaging Development	**Packaging Development**	**Production**	**Regulatory Affairs**	**Quality Assurance**

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 and PV related queries to

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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 90 mg/400 mg film coated tablets. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis 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

Pharmacotherapeutic group: Direct-acting antiviral; ATC code: J05A P51

5.1 Mechanism of action

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.

5.2 Pharmacodynamic properties

Antiviral activity

The EC50 values of Ledipasvir and Sofosbuvir against full-length or chimeric replicons encoding NS5A and NS5B sequences from clinical isolates are detailed in Table 6. 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 6: Activity of Ledipasvir and Sofosbuvir against chimeric replicons

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

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

Resistance

In cell culture

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

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

In clinical studies – Genotype 1

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

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients (22/29 genotype 1a and 7/8 genotype 1b) not achieving sustained virologic response (SVR). Of the 29 genotype 1a patients who qualified for resistance testing, 22/29 (76%) patients harboured one or more NS5A RAVs at positions K24, M28, Q30, L31, S38 and Y93 at failure, while the remaining 7/29 patients had no NS5A RAVs detected at failure. The most common variants were Q30R, Y93H and L31M. Of the 8 genotype 1b patients who qualified for resistance testing, 7/8 (88%) harboured one or more NS5A RAVs at positions L31 and Y93 at failure, while 1/8 patients had no NS5A RAVs at failure. The most common variant was Y93H. Among the 8 patients who had no NS5A RAVs at failure, 7 patients received 8 weeks of treatment (n = 3 with ledipasvir/sofosbuvir; n = 4 with ledipasvir/sofosbuvir + ribavirin) and 1 patient received ledipasvir/sofosbuvir for 12 weeks. In phenotypic analyses, post-baseline isolates from patients who harboured NS5A RAVs at failure showed 20- to at least a 243-fold (the highest dose tested) reduced susceptibility to ledipasvir. Site-directed mutagenesis of the Y93H substitution in both genotype 1a and 1b as well as the Q30R and L31M substitution in genotype 1a conferred high levels of reduced susceptibility to ledipasvir (fold-change in EC50 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]).

Effect of baseline HCV resistance-associated variants on treatment outcome

Genotype 1

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

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

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

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 posttransplant), 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

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 7: 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 8: 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 9: 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 10: Demographics and baseline characteristics in study ION-1

Patient disposition	LDV/SOF 12 weeks (n = 214)	LDV/SOF+ RBV 12 weeks (n = 217)	LDV/SOF24 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 11: 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	0/213a	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 12: 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 13: 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 14 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 14: 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 EC50 (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 15: 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 16). 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/m2 (range: 18 to 49 kg/m²); 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 16: 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)
	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

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.

5.3 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 $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$ and C_{max} were similar in healthy adult subjects and patients with HCV infection. Relative to healthy subjects (n = 191), ledipasvir $AUC_{0\text{-}24}$ 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 AUC0-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 90 mg/400 mg film coated tablets 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 [14C]-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 90 mg/400 mg film coated tablets compared to subjects with normal renal function, as described in the text below, are provided in Table 17.

Table 17: 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/1.73m²)	Moderate RI (eGFR ≥30 and <50 mL/min/ 1.73 m²)	Severe RI (eGFR <30 mL/ min/1.73 m²)	ESRD Requiring Dialysis Dosed 1 hr After Dialysis		Severe RI (eGFR < 30 mL/ min/ 1.73m²)	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 (AUCinf) 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 $AUC_{0\text{-}24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected 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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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.

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.

7. DESCRIPTION

Film-coated tablet.

Ledipasvir and Sofosbuvir 90 mg/400 mg tablets are light blue, oval shaped, biconvex, beveled edge film coated tablets debossed with "LSF" on one side of the tablet and "M" on the other side.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Refer to pack

8.3 Packaging information

Ledipasvir and Sofosbuvir 90 mg/400 mg tablets are packed in High Density Polyethylene (HDPE) bottle with induction sealed closure. Each bottle contains 28 tablets with silica gel desiccant.

8.4 Storage and handling instructions

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

9. Patient Counselling Information

Ledipasvir and Sofosbuvir 90 mg/400 mg film-coated tablets (MyHep LVIR®)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet

1. What Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is and what it is used for
2. What you need to know before you take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets
3. How to take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets
4. Possible side effects
5. How to store Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets
6. Contents of the pack and other information

1. What Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is and what it is used for

Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is a medicine that contains the active substances ledipasvir and sofosbuvir. Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is given for the treatment of chronic hepatitis C virus (CHC) genotype 1 infection in **adults**.

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

Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is sometimes taken with another medicine, ribavirin.

It is very important that you also read the leaflets for the other medicines that you will be taking with Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets. If you have any questions about your medicines, please ask your doctor or pharmacist.

2. What you need to know before you take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets

Do not take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets

- **If you are allergic** to ledipasvir, sofosbuvir or any of the other ingredients of this medicine (listed in section 6 of this leaflet).
- **If you are currently taking any of the following medicines:**
  - **rifampicin and rifabutin** (antibiotics used to treat infections, including tuberculosis);
  - **St. John's wort** (herbal medicine used to treat depression);
  - **carbamazepine, phenobarbital and phenytoin** (medicines used to treat epilepsy and prevent seizures);
  - **rosuvastatin** (a medicine used to treat high cholesterol).

→ If any of these conditions applies to you, **do not take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets and tell your doctor immediately.**

Warnings and precautions

Your doctor will know if any of the following conditions apply to you. These will be considered before treatment with Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is started.

- **other liver problems** apart from hepatitis C, for instance
  - **if you are awaiting a liver transplant;**
  - **if you have a current or previous infection with the hepatitis B virus,** since your doctor may want to monitor you more closely;
- **kidney problems or if you are on kidney dialysis**, since Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets has not been fully tested in patients with severe kidney problems;
- **ongoing treatment for HIV infection**, since your doctor may want to monitor you more closely.

Talk to your doctor or pharmacist before taking Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets if:

- you currently take, or have taken in the last few months, the medicine amiodarone to treat irregular heartbeats, as it may result in a life-threatening slowing of your heart beat. Your doctor may consider different treatments if you have taken this medicine. If treatment with Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets is needed, you may require additional heart monitoring.
- you have diabetes. You may need closer monitoring of your blood glucose levels and/or adjustment of your diabetes medication after starting Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets. Some diabetic patients have experienced low sugar levels in the blood (hypoglycaemia) after starting treatment with medicines like Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets

Tell your doctor immediately if you currently take, or have taken in the last months, any medicines for heart problems and during treatment you experience:

- slow or irregular heartbeat, or heart rhythm problems;
- shortness of breath or worsening of existing shortness of breath;
- chest-pain;
- light-headedness
- palpitations
- near fainting or fainting

Blood tests

Your doctor will test your blood before, during and after your treatment with Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets. This is so that:

- Your doctor can decide if you should take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets and for how long;
- Your doctor can confirm that your treatment has worked and you are free of the hepatitis C virus.

Children and adolescents

Do not give this medicine to children and adolescents aged less than 18 years of age. Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets are not recommended in children and adolescents aged less than 18 years of age.

Other medicines and Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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

Your liver function may change with treatment of hepatitis C and therefore may affect other medications (e.g. medicines used to suppress your immune system, etc.). Your doctor may need to closely monitor these other medicines you are taking and make adjustments after starting Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets.

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

Some medicines should not be taken with Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets

- **Do not take any other medicine that contains sofosbuvir, one of the active substances in Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets.**
- **Tell your doctor or pharmacist** if you are taking any of the medicines below:
  - **amiodarone** used to treat irregular heartbeats;
  - **tenofovir disoproxil fumarate** or any medicine containing tenofovir disoproxil fumarate, used to treat HIV infection;
  - **digoxin** used to treat heart conditions;
  - **dabigatran** used to thin the blood;
  - **statins** used to treat high cholesterol;
  - **rifapentine** (antibiotic used to treat infections, including tuberculosis);
  - **oxcarbazepine** (a medicine used to treat epilepsy and prevent seizures);
  - **tipranavir** (used to treat HIV infection).

Taking Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets with any of these may stop your medicines from working properly, or make any side effects worse. Your doctor may need to give you a different medicine or adjust the dose of medicine you are taking.

- **Get advice from a doctor or pharmacis**t if you take medicines used to treat **stomach ulcers, heartburn or acid reflux**. This includes:
  - antacids (such as aluminium/magnesium hydroxide or calcium carbonate). These should be taken at least 4 hours before or 4 hours after Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets;
  - proton pump inhibitors (such as omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole). These should be taken at the same time as Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets. Do not take proton pump inhibitors before Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets. Your doctor may give you a different medicine or adjust the dose of the medicine you are taking;
  - H_2-receptor antagonists (such as famotidine, cimetidine, nizatidine or ranitidine). Your doctor may give you a different medicine or adjust the dose of the medicine you are taking

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

Pregnancy and contraception

The effects of Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets during pregnancy are not known. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy must be avoided if Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is taken together with ribavirin. It is very important that you read the "Pregnancy" section in the ribavirin package leaflet very carefully. Ribavirin can be very damaging to an unborn baby. Therefore, special precautions in sexual activity must be taken if there is any chance for pregnancy to occur.

- You or your partner must use an effective birth control method during treatment with Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets together with ribavirin and for some time afterwards. It is very important that you read the "Pregnancy" section in the ribavirin package leaflet very carefully. Ask your doctor for an effective contraceptive method suitable for you.
- If you or your partner become pregnant during Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets and ribavirin treatment or in the months that follow, you must contact your doctor immediately.

Breast-feeding

Do not breast-feed during treatment with Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets. It is not known whether ledipasvir or sofosbuvir, the two active substances of Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets, pass into human breast milk.

Driving and using machines

If you feel tired after taking Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets you should not take part in activities that require concentration, for example, do not drive, ride a bike or operate machines.

Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets contains lactose

- **If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.**
- **Ledipasvir/Sofosbuvir 90 mg/400 mg film coated tablets contains Opadry blue which may cause allergic reactions.**

Tell your doctor if you are allergic to Opadry blue before taking this medicine.

3. How to take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets

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

Recommended dose

Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets is to be taken as advised by your doctor. The recommended dose of Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets **in adults is one 90 mg/400 mg film-coated tablet once a day.** Your doctor will tell you for how many weeks you should take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets.

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

I**f you are taking an antacid**, take it at least 4 hours before or at least 4 hours after Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets.

If you are taking a proton pump inhibitor, take the proton pump inhibitor at the same time as Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets. Do not take it before Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets.

If you are sick (vomit) after taking Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets it may affect the amount of Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets in your blood. This may make Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets work less well.

- If you are sick (vomit) **less than 5 hours after** taking Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets, take another dose.
- If you are sick (vomit) **more than 5 hours after** taking Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets, you do not need to take another dose until your next scheduled dose.

If you take more Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets than you should

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

If you forget to take Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets

It is important not to miss a dose of this medicine.

If you do miss a dose, work out how long it is since you last took your Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets:

- **If you notice within 18 hours** of the time you usually take Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets, you must take the dose as soon as possible. Then take the next dose at your usual time.
- **If it's 18 hours or more** after the time you usually take Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets, wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

Do not stop taking Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets

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

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

4. Possible side effects

Like all medicines, this medicine may cause side effects. If you take Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets you may get one or more of the side effects below:

Very common side effects

(may affect more than 1 in 10 people)

- headache
- feeling tired

Common side effects

(may affect up to 1 in 10 people)

- rash

Other effects that may be seen during treatment with Ledipasvir/ sofosbuvir 90 mg/400 mg film-coated tablets

The frequency of the following side effects is not known (frequency cannot be estimated from the available data).

- swelling of the face, lips, tongue or throat (angioedema).

Other effects that may be seen during treatment with sofosbuvir:

The frequency of the following side effects is not known (frequency cannot be estimated from the available data).

- a wide-spread severe rash with peeling skin which may be accompanied by fever, flu-like symptoms, blisters in the mouth, eyes, and/or genitals (Stevens-Johnson syndrome).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine. For reporting side effects, please contact:

Mylan Pharmaceuticals Private Limited
10th Floor, Prestige Platina, Block 3,
Kadubeesanahalli Village,
Varthur Hobli, Outer Ring Road,
Bangalore East Taluk, Bangalore 560 087, India
Email: ProductSafety@viatris.com

5.How to store Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets

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

6. Contents of the pack and other information

What Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets contains

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

  Tablet core:

  Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Colloidal silicon dioxide, Magnesium stearate

  Film-coating

  Polyvinyl alcohol, Titanium dioxide IP, Macrogol / PEG, Talc, Indigo carmine, Aluminum lake

What Ledipasvir/sofosbuvir 90 mg/400 mg film-coated tablets looks like and contents of the pack

Film-coated tablet.

Ledipasvir and Sofosbuvir 90 mg/400 mg tablets are Light blue, Oval shaped, biconvex, beveled edge film coated tablets debossed with "LSF" on one side of the tablet and "M" on the other side.

10. DETAILS OF MANUFACTURER

Manufactured by:

Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik-422113, Maharashtra, INDIA

Marketed by:

Mylan Pharmaceuticals Pvt. Ltd.
Room No. 2, Minus 3rd Floor,
Plot No. 564/A/22, Road No. 92,
Jubilee Hills, Ameerpet, Hyderabad,
Telangana – 500 096, INDIA

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing. Licence. No.: NKD/89

12. DATE OF REVISION

August 2021

MyHep LVIR® 90 mg/400 mg is manufactured under license from M/s Gilead Sciences Ireland UC

REFERENCES:

1. Harvoni [EMEA Summary of Product Characteristics] (Gilead Sciences Ireland UC); July 2021; Available from:
https://www.ema.europa.eu/en/documents/product-information/harvoni-epar-product-information_en.pdf
Accessed on July 22nd, 2021.
2. Harvoni [EMEA Package Leaflet] (Gilead Sciences Ireland UC); July 2021; Available from:
https://www.ema.europa.eu/en/documents/product-information/harvoni-epar-product-information_en.pdf
Accessed on July 22nd, 2021.

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Mylan Laboratories Limited Packaging Development	Artwork Implementation Schedule Check (✓) whichever is applicable (Approval is not valid without following details)	Date of Issue		Issued By	
		Date of Return			
		Material Code	75080656 Supersedes 75068906	Market	MYLAN-INDIA
[ ] New Component [ ] Immediately (Stock of superseded component to be destroyed, if applicable.) [ ] After consumption of existing (superseded) stock. [ ] Other (Specify)		Description	LIT. MYHEP LVIR TABS 90 mg/400 mg MYLAN-INDIA V3		
		Component	Printed Literature	Actual Size	Flat- 400 x 680 mm; Folded- 35 x 51 mm
		Substrate	40gsm ITC Tribeni Paper		
		Design & Style	Supply in Folded form as Proposed Size (with tape)		
Sign. dd/mm/yy Job Function	Sign. dd/mm/yy Job Function / Sign. dd/mm/yy Job Function	Reason for Issue	Change in Text and Size		

Printing Pantone Nos	1	BLACK	2	NA	3	NA	4	NA
	5	NA	6	NA	7	NA	8	NA
Non Printing	●	Die Line	○	NA	○	NA	○	NA

Proof No.	1	2	3	4	5
Date	30.07.2021	17.08.2021	dd/mm/yy	dd/mm/yy	dd/mm/yy
Remarks	Revised a/w.	Corrections 03.08	x	x	x

SOP-000565164-FORM-000565208-A01-03-01-20 | **Final Date** dd-mm-yy

Prepared By	Checked By		Approved By	
Packaging Development	Packaging Development	Production	Regulatory Affairs	Quality Assurance