LISOF
90 mg / 400 mg
2065425

℞

LEDIPASVIR + SOFOSBUVIR

LISOF
90 mg / 400 mg film-coated tablet
Antiviral

FORMULATION:

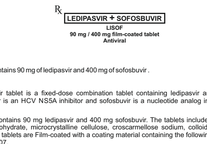
Each film coated tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir .

DRUG DESCRIPTION

Ledipasvir and sofosbuvir tablet is a fixed-dose combination tablet containing ledipasvir and sofosbuvir for oral administration. Ledipasvir is an HCV NS5A inhibitor and sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase.

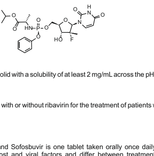
Each film coated tablet contains 90 mg ledipasvir and 400 mg sofosbuvir. The tablets include the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The tablets are Film-coated with a coating material containing the following inactive ingredients: Opadry II Brown:85F565007.

Ledipasvir: The IUPAC name for ledipasvir is Methyl [(2S)-1-((6S)-6-[5-(9,9-difluoro-7- (2-{(1R,3S,4S)-2-[(2S)-2-{(methoxycarbonyl)amino}-3-methylbutanoyl]-2-azabicyclo[2.2.1]hept-5-yl}-1H-benzimidazol-6-yl)-9H-fluoren-2-yl}-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl)-3-methyl-1-oxobutan-2-yl]carbamate. It has a molecular formula of $C_{49}H_{54}F_2N_8O_6$ and a molecular weight of 889.00. It has the following structural formula:



It Ledipasvir is practically insoluble (less than 0.1 mg/mL) across the pH range of 3.0–7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL).

Sofosbuvir: The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-((2R,3R,4R,5R)-5- (2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. It has the following structural formula:



Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37°C and is slightly soluble in water.

THERAPEUTIC INDICATIONS

Ledipasvir and Sofosbuvir tablet is indicated with or without ribavirin for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1, 4, 5, or 6 infection.

DOSAGE AND ADMINISTRATION

Recommended Dosage in Adults

The recommended dosage of Ledipasvir and Sofosbuvir is one tablet taken orally once daily with or without food. Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups. Table 1 shows the recommended Ledipasvir and Sofosbuvir tablet treatment regimen and duration based on patient population. For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1. Refer to Drug Interactions for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 Recommended Treatment Regimen and Duration for Ledipasvir and Sofosbuvir tablet in Patients with Genotype 1, 4, 5 or 6 HCV

	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naive without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Ledipasvir and Sofosbuvir 12 weeks*
	Treatment-experienced† without cirrhosis	Ledipasvir and Sofosbuvir 12 weeks
	Treatment-experienced† with compensated cirrhosis (Child-Pugh A)	Ledipasvir and Sofosbuvir 24 weeks‡
	Treatment-naive and treatment-experienced† with decompensated cirrhosis (Child-Pugh B or C)	Ledipasvir +Sofosbuvir and ribavirin§ 12 weeks
Genotype 1 or 4	Treatment-naive and treatment-experienced†, liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	Ledipasvir +Sofosbuvir and ribavirin§ 12 weeks
Genotype 4, 5 or 6	Treatment-naive and treatment-experienced† without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Ledipasvir and Sofosbuvir 12 weeks

* Ledipasvir and Sofosbuvir tablet for 8 weeks can be considered in treatment-naïve genotype1patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

† Treatment-experienced patients include those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor.

‡ Ledipasvir and Sofosbuvir tablet ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin. See footnote

¶ for ribavirin dosage recommendations.

§ In patients with decompensated cirrhosis, the starting dosage of ribavirin is 600 mg and can be titrated up to 1000 mg for patients <75 kg and 1200 mg for those ≥75 kg in two divided doses with food. If the starting dosage of ribavirin is not well tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels.

¶ The daily dosage of ribavirin is weight-based (1000 mg for patients <75 kg and 1200 mg for those ≥75 kg) administered orally in two divided doses with food.

Severe Renal Impairment and End Stage Renal Disease

No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73m2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

CONTRAINDICATIONS

If Ledipasvir and Sofosbuvir tablet is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.

WARNINGS AND PRECAUTIONS

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with Ledipasvir and Sofosbuvir tablet. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with Ledipasvir and Sofosbuvir tablet is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered Ledipasvir and Sofosbuvir tablet:

- Counsel patients about the risk of serious symptomatic bradycardia
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, 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.

Patients who are taking Ledipasvir and Sofosbuvir tablet who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting Ledipasvir and Sofosbuvir should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Risk of Reduced Therapeutic Effect Due to Use with P-gp Inducers

The concomitant use of Ledipasvir and Sofosbuvir tablet and P-gp inducers (e.g., rifampin, St. John's wort) may significantly decrease ledipasvir and sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of Ledipasvir and Sofosbuvir tablet. Therefore, the use of Ledipasvir and Sofosbuvir tablet with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Risks Associated with Ribavirin Combination Treatment

If Ledipasvir and Sofosbuvir tablet is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

Related Products Not Recommended

The use of Ledipasvir and Sofosbuvir tablet with other products containing sofosbuvir is not recommended.

ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

If Ledipasvir and Sofosbuvir tablet is administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions.

The safety assessment of Ledipasvir and Sofosbuvir tablet was based on pooled data from three randomized, open-label Phase 3 clinical trials (ION-3, ION-1 and ION-2) of subjects with genotype 1 HCV with compensated liver disease (with and without cirrhosis) including 215, 539, and 326 subjects who received Ledipasvir and Sofosbuvir tablet once daily by mouth for 8, 12 and 24 weeks, respectively.

The proportion of subjects who permanently discontinued treatment due to adverse events was 0%, less than 1%, and 1% for subjects receiving Ledipasvir and Sofosbuvir tablet for 8, 12, and 24 weeks, respectively.

The most common adverse reactions (at least 10%) were fatigue and headache in subjects treated with 8, 12, or 24 weeks of Ledipasvir and Sofosbuvir tablet.

Table 2 lists adverse reactions (adverse events assessed as causally related by the investigator, all grades) observed in at least 5% of subjects receiving 8, 12, or 24 weeks treatment with Ledipasvir and Sofosbuvir tablet in clinical trials. The majority of adverse reactions presented in Table 2 occurred at severity of grade 1. The side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

Table 2 Adverse Reactions (All Grades) Reported in ≥5% of Subjects Receiving 8, 12, or 24 Weeks of Treatment with Ledipasvir and Sofosbuvir tablet

	Ledipasvir and Sofosbuvir tablet 8 weeks	Ledipasvir and Sofosbuvir tablet 12 weeks	Ledipasvir and Sofosbuvir tablet 24 weeks
	N=215	N=539	N=326
Fatigue	16%	13%	18%
Headache	11%	14%	17%
Nausea	6%	7%	9%
Diarrhea	4%	3%	7%
Insomnia	3%	5%	6%

The safety assessment of Ledipasvir and Sofosbuvir tablet was also based on pooled data from three open-label trials (Study 1119, ION-4 and ELECTRON-2) in 118 subjects with chronic HCV genotype 4, 5 or 6 infection with compensated liver disease (with or without cirrhosis). The subjects received Ledipasvir and Sofosbuvir tablet once daily by mouth for 12 weeks. The safety profile in subjects with chronic HCV genotype 4, 5 or 6 infection with compensated liver disease was similar to that observed in subjects with chronic HCV genotype 1 infection with compensated liver disease. The most common adverse reactions occurring in at least 10% of subjects were asthenia (18%), headache (14%) and fatigue (10%).

Adverse Reactions in Subjects with Cirrhosis

The safety assessment of Ledipasvir and Sofosbuvir tablet with or without ribavirin was based on a randomized, double-blind and placebo-controlled trial in treatment-experienced genotype 1 subjects with compensated cirrhosis and was compared to placebo in the SIRIUS trial. Subjects were randomized to receive 24 weeks of Ledipasvir and Sofosbuvir tablet once daily by mouth without ribavirin or 12 weeks of placebo followed by 12 weeks of Ledipasvir and Sofosbuvir tablet once daily by mouth + ribavirin.

Table 3 presents the adverse reactions, as defined above, that occurred with at least 5% greater frequency in subjects treated with 24 weeks of Ledipasvir and Sofosbuvir tablet or 12 weeks of Ledipasvir and Sofosbuvir tablet + ribavirin, compared to those reported for 12 weeks of placebo. The majority of the adverse reactions presented in Table 3 were Grade 1 or 2 in severity.

Table 3 Adverse Reactions with ≥5% Greater Frequency Reported in Treatment-Experienced Subjects with Cirrhosis Receiving Ledipasvir and Sofosbuvir tablet for 24 Weeks or Ledipasvir and Sofosbuvir tablet +RBV for 12 Weeks Compared to Placebo for 12 weeks

	Ledipasvir and Sofosbuvir tablet 24 weeks (N=78)	Ledipasvir and Sofosbuvir tablet +RBV 12 weeks (N=76)	Placebo 12 weeks (N=77)
Asthenia	31%	36%	23%
Headache	29%	13%	16%
Fatigue	18%	4%	1%
Cough	5%	11%	1%
Myalgia	0%	4%	0%
Dyspnea	3%	9%	1%
Irritability	8%	7%	1%
Dizziness	5%	1%	0%

Adverse Reactions in Subjects Co-infected with HIV-1

The safety assessment of Ledipasvir and Sofosbuvir tablet was based on an open-label clinical trial in 335 genotype 1 or 4 subjects with HCV/HIV-1 coinfection who were on stable antiretroviral therapy in Study ION-4. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. The most common adverse reactions occurring in at least 10% of subjects were headache (20%) and fatigue (17%).

Adverse Reactions in Liver Transplant Recipients and/or Subjects with Decompensated Cirrhosis

The safety assessment of Ledipasvir and Sofosbuvir tablet with ribavirin (RBV) in liver transplant recipients and/or those who had decompensated liver disease was based on pooled data from two Phase 2 open-label clinical trials including 336 subjects who received Ledipasvir and Sofosbuvir tablet + RBV for 12 weeks. Subjects with Child-Pugh-Turcotte (CPT) scores greater than 12 were excluded from the trials.

The adverse events observed were consistent with the expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known safety profile of Ledipasvir and Sofosbuvir Tablet and/or ribavirin.

Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 38% and 13% of subjects treated with Ledipasvir and Sofosbuvir tablet + RBV for 12 weeks, respectively. Ribavirin was permanently discontinued in 11% of subjects treated with Ledipasvir and Sofosbuvir tablet plus RBV for 12 weeks.

Liver Transplant Recipients with Compensated Liver Disease:

Among the 174 liver transplant recipients with compensated liver disease who received Ledipasvir and Sofosbuvir tablet with RBV for 12 weeks, 2 (1%) subjects permanently discontinued Ledipasvir and Sofosbuvir tablet due to an adverse event.

Subjects with Decompensated Liver Disease:

Among the 162 subjects with decompensated liver disease (pre- or post-transplant) who received Ledipasvir and Sofosbuvir tablet with RBV for 12 weeks, 7 (4%) subjects died, 4 (2%) subjects underwent liver transplantation, and 1 subject (<1%) underwent liver transplantation and died during treatment; all within 30 days after discontinuation of treatment. Because these events occurred in patients with advanced liver disease who are at risk of progression of liver disease including liver failure and death, it is not possible to reliably assess the contribution of drug effect to outcomes. A total of 4 (2%) subjects permanently discontinued Ledipasvir and Sofosbuvir tablet due to an adverse event.

Less Common Adverse Reactions Reported in Clinical Trials (less than 5%): The following adverse reactions occurred in less than 5% of subjects receiving Ledipasvir and sofosbuvir tablet in any one trial. These events have been included because of their seriousness or assessment of potential causal relationship.

Psychiatric disorders: depression (including in subjects with pre-existing history of psychiatric illness).

Depression (particularly in subjects with pre-existing history of psychiatric illness) occurred in subjects receiving sofosbuvir containing regimens. Suicidal ideation and suicide have occurred in less than 1% of subjects treated with sofosbuvir in combination with ribavirin or pegylated interferon/ribavirin in other clinical trials.

Laboratory Abnormalities

Bilirubin Elevations: Bilirubin elevations of greater than 1.5×ULN were observed in 3%, less than 1%, and 2% of subjects treated with Ledipasvir and Sofosbuvir Tablet for 8, 12, and 24 weeks, respectively. Bilirubin elevations of greater than 1.5×ULN were observed in 3%, 11% and 3% of subjects with compensated cirrhosis treated with placebo, Ledipasvir and Sofosbuvir Tablet + ribavirin for 12 weeks and Ledipasvir and Sofosbuvir tablet for 24 weeks, respectively, in the SIRIUS trial.

Lipase Elevations: Transient, asymptomatic lipase elevations of greater than 3×ULN were observed in less than 1%, 2%, and 3% of subjects treated with Ledipasvir and Sofosbuvir tablet for 8, 12, and 24 weeks, respectively. Transient, asymptomatic lipase elevations of greater than 3× ULN were observed in 1%, 3% and 9% of subjects with compensated cirrhosis treated with placebo, Ledipasvir and Sofosbuvir tablet + ribavirin for 12 weeks and Ledipasvir and Sofosbuvir tablet for 24 weeks, respectively, in the SIRIUS trial.

Creatine Kinase: Creatine kinase was not assessed in Phase 3 trials ION-3, ION-1 or ION-2 of Ledipasvir and Sofosbuvir tablet. Creatine kinase was assessed in the ION-4 trial. Isolated, asymptomatic creatine kinase elevations of greater than or equal to 10×ULN was observed in 1% of subjects treated with Ledipasvir and Sofosbuvir tablet for 12 weeks in the ION-4 trial and has also been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Ledipasvir and Sofosbuvir tablet. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with Ledipasvir and Sofosbuvir tablet.

Skin and Subcutaneous Tissue Disorders

Skin rashes, sometimes with blisters or angioedema-like swelling

DRUG INTERACTIONS

Potential for Drug Interaction

As Ledipasvir and Sofosbuvir tablet contains ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with Ledipasvir and Sofosbuvir tablet. After oral administration of Ledipasvir and Sofosbuvir tablet, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both sofosbuvir and the inactive metabolite GS-331007 were monitored for purposes of pharmacokinetic analyses.

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters.

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. P-gp inducers (e.g., rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations, leading to reduced therapeutic effect of Ledipasvir and Sofosbuvir tablet, and the use with P-gp inducers is not recommended with Ledipasvir and Sofosbuvir tablet.

Established and Potentially Significant Drug Interactions

Table 4 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either Ledipasvir and Sofosbuvir tablet, the components of Ledipasvir and Sofosbuvir tablet as individual agents, or are predicted drug interactions that may occur with Ledipasvir and Sofosbuvir tablet.

Table 4 Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction*

Concomitant Drug Class: Drug Name	Effect on Concentration†	Clinical Comment
Acid Reducing Agents:	↓ ledipasvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		It is recommended to separate antacid and Ledipasvir and Sofosbuvir tablet administration by 4 hours.
H2-receptor antagonists‡ (e.g., famotidine)		H2-receptor antagonists may be administered simultaneously with or 12 hours apart from Ledipasvir and Sofosbuvir tablet at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors‡ (e.g., omeprazole)		Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with Ledipasvir and Sofosbuvir tablet under fasted conditions.
Antiarrhythmics: amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Coadministration of amiodarone with Ledipasvir and Sofosbuvir tablet may result in serious symptomatic bradycardia. The mechanism of this interaction is unknown. Coadministration of amiodarone with Ledipasvir and Sofosbuvir tablet is not recommended; if coadministration is required, cardiac monitoring is recommended
digoxin	↑ digoxin	Coadministration of Ledipasvir and Sofosbuvir tablet with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended when coadministered with Ledipasvir and Sofosbuvir tablet
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir	Coadministration of Ledipasvir and Sofosbuvir tablet with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Ledipasvir and Sofosbuvir tablet . Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin‡ rifapentine	↓ ledipasvir ↓ sofosbuvir	Coadministration of Ledipasvir and Sofosbuvir tablet with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Ledipasvir and Sofosbuvir tablet. Coadministration is not recommended. Coadministration of Ledipasvir and Sofosbuvir tablet with rifampin, a P-gp inducer, is not recommended
HIV Antiretrovirals:		
Regimens containing tenofovir DF without a HIV protease inhibitor/ritonavir or cobicistat	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving Ledipasvir and Sofosbuvir tablet concomitantly with a regimen containing tenofovir DF without a HIV protease inhibitor/ritonavir or cobicistat.
Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir or cobicistat o atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF‡ o darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF‡ o lopinavir/ritonavir + emtricitabine/tenofovir DF‡	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of Ledipasvir and Sofosbuvir tablet or a HIV protease inhibitor/ritonavir or cobicistat, has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions.
elvitegravir, cobicistat, emtricitabine, tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of Ledipasvir and Sofosbuvir tablet and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Coadministration is not recommended.
ritonavir/ritonavir	↓ ledipasvir ↓ sofosbuvir	Coadministration of Ledipasvir and Sofosbuvir tablet with ritonavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Ledipasvir and Sofosbuvir tablet. Coadministration is not recommended.
HCV Products: simeprevir‡	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. Coadministration of Ledipasvir and Sofosbuvir tablet with simeprevir is not recommended.
Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ ledipasvir ↓ sofosbuvir	Coadministration of Ledipasvir and Sofosbuvir tablet with St. John's wort, a P-gp inducer is not recommended
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration of Ledipasvir and Sofosbuvir tablet with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of Ledipasvir and Sofosbuvir tablet with rosuvastatin is not recommended.

enofovir DF = tenofovir disoproxil fumarate

* This table is not all inclusive.

† ↓ = decrease, ↑ = increase

‡ These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with Ledipasvir and Sofosbuvir tablet

Based on drug interaction studies conducted with the components of ledipasvir or sofosbuvir tablet or ledipasvir or sofosbuvir tablet, no clinically significant drug interactions have been either observed or are expected when ledipasvir or sofosbuvir tablet is used with the following drugs abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, or verapamil See Table 4 for use of Ledipasvir and Sofosbuvir tablet with certain HIV antiretroviral regimens.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

No adequate human data are available to establish whether or not Ledipasvir and Sofosbuvir tablet poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of ledipasvir or sofosbuvir tablet at exposures greater than those in humans at the recommended human dose (RHD). During organogenesis in the rat and rabbit, systemic exposures (AUC) to ledipasvir were approximately 4 (rats) and 2 (rabbits) times the exposure in humans at the RHD, while exposures to the predominant circulating metabolite of sofosbuvir (GS-331007) were ≥3 (rats) and 7 (rabbits) times the exposure in humans at the RHD. In rat pre/postnatal development studies, maternal systemic exposures (AUC) to ledipasvir and GS-331007 were approximately 5 and 7 times, respectively, the exposure in humans at the RHD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

If Ledipasvir and Sofosbuvir tablet is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant.

Data

Animal Data

Ledipasvir: Ledipasvir was administered orally to pregnant rats (up to 100 mg/kg/day) and rabbits (up to 180 mg/kg/day) on gestation days 6 to 18 and 7 to 20, respectively, and also to rats (oral doses up to 100 mg/kg/day) on gestation day 6 to lactation/ post-partum day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. Systemic exposures (AUC) to ledipasvir were ≥4 (rats) and 2 (rabbits) times the exposure in humans at the RHD.

Sofosbuvir: Sofosbuvir was administered orally to pregnant rats (up to 500 mg/kg/day) and rabbits (up to 300 mg/kg/day) on gestation days 6 to 18 and 6 to 19, respectively, and also to rats (oral doses up to 500 mg/kg/day) on gestation day 6 to lactation/post-partum day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. Systemic exposures (AUC) to the predominant circulating metabolite of sofosbuvir (GS-331007) were ≥3 (rats) and 7 (rabbits) times the exposure in humans at the RHD, with exposures increasing during gestation from approximately 3 to 6 (rats) and 7 to 17 (rabbits) times the exposure in humans at the RHD.

Lactation

Risk Summary

It is not known whether Ledipasvir and Sofosbuvir tablet and its metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. When administered to lactating rats, ledipasvir was detected in the plasma of nursing pups likely due to the presence of ledipasvir in milk, without clear effects on nursing pups. The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Ledipasvir and sofosbuvir tablet and any potential adverse effects on the breastfed child from Ledipasvir and sofosbuvir tablet or from the underlying maternal condition.

If Ledipasvir and sofosbuvir tablet is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use during lactation.

Data

Ledipasvir: No effects of ledipasvir on growth and postnatal development were observed in nursing pups at the highest dose tested. Maternal systemic exposure (AUC) to ledipasvir was approximately 5 times the exposure in humans at the RHD. Although not measured directly, ledipasvir was likely present in the milk of lactating rats, since systemic exposure (AUC) to ledipasvir of approximately 25% that of maternal exposure was observed in nursing pups on lactation day 10.

Sofosbuvir: No effects of sofosbuvir on growth and postnatal development were observed in nursing pups at the highest dose tested. Maternal systemic exposure (AUC) to the predominant circulating metabolite of sofosbuvir (GS-331007) was approximately 7 times the exposure in humans at the RHD, with exposure of approximately 2% that of maternal exposure observed in nursing pups on lactation day 10. In a lactation study, sofosbuvir metabolites (primarily GS-331007) were excreted into the milk of lactating rats following administration of a single oral dose of sofosbuvir (20 mg/kg) on lactation day 2, with milk concentrations of approximately 10% that of maternal plasma concentrations observed 1 hour post-dose.

Females and Males of Reproductive Potential

If Ledipasvir and Sofosbuvir tablet is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen.

Pediatric Use

Safety and effectiveness of Ledipasvir and Sofosbuvir tablet have not been established in pediatric patients.

Geriatric Use

Size: 240x670mm
Pharmacode: Front-2315 & Back-2316
No.of colors: 01, Black

Nonprinting colors:
Diecut

Note: Position, Height of the pharma code are tentative, it can be changed based on folding size.

Clinical trials of Ledipasvir and Sofosbuvir tablet included 225 subjects aged 65 and over (9% of total number of subjects in the clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of Ledipasvir and Sofosbuvir tablet is warranted in geriatric patients.

Renal Impairment

No dosage adjustment of Ledipasvir and sofosbuvir tablet is required for patients with mild or moderate renal impairment. The safety and efficacy of Ledipasvir and Sofosbuvir tablet have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m^2) or ESRD requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Hepatic Impairment

No dosage adjustment of Ledipasvir and Sofosbuvir tablet is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C.

Clinical and hepatic laboratory monitoring, as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with Ledipasvir + Sofosbuvir tablet and ribavirin.

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Ledipasvir and Sofosbuvir tablet is a fixed-dose combination of ledipasvir and sofosbuvir which are direct-acting antiviral agents against the hepatitis C virus.

Pharmacodynamics

Cardiac Electrophysiology

Thorough QT studies have been conducted for ledipasvir and sofosbuvir.

The effect of ledipasvir 120 mg twice daily (2.67 times the maximum recommended dosage) for 10 days on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three period crossover thorough QT trial in 59 healthy subjects. At the dose of 120 mg twice daily (2.67 times the maximum recommended dosage), ledipasvir does not prolong QTc interval to any clinically relevant extent.

The effect of sofosbuvir 400 mg (maximum recommended dosage) and 1200 mg (three times the maximum recommended dosage) on QTc interval was evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects. At a dose three times the maximum recommended dose, sofosbuvir does not prolong QTc to any clinically relevant extent.

Pharmacokinetics

Absorption

The pharmacokinetic properties of ledipasvir, sofosbuvir, and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Following oral administration of Ledipasvir and Sofosbuvir tablet, ledipasvir median peak concentrations were observed 4 to 4.5 hours post-dose. Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed ~0.8 to 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.5 to 4 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected subjects, geometric mean steady-state AUC_{0-24} for ledipasvir (N=2113), sofosbuvir (N=1542), and GS-331007 (N=2113) were 7290, 1320, and 12,000 ng•hr/mL, respectively. Steady-state Cmax for ledipasvir, sofosbuvir, and GS-331007 were 323, 618, and 707 ng/mL, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and subjects with HCV infection. Relative to healthy subjects (N=191), ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively, in HCV-infected subjects.

Effect of Food

Relative to fasting conditions, the administration of a single dose of Ledipasvir and Sofosbuvir tablet with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal increased sofosbuvir AUC0–inf by approximately 2-fold, but did not significantly affect sofosbuvir C_{max}. The exposures of GS-331007 and ledipasvir were not altered in the presence of either meal type. The response rates in Phase 3 trials were similar in HCV-infected subjects who received Ledipasvir and Sofosbuvir tablet with food or without food. Ledipasvir and Sofosbuvir tablet can be administered without regard to food.

Distribution

Ledipasvir is greater than 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 microgram/mL to 20 microgram/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.

Metabolism

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

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately greater than 90% 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 feces and urine was approximately 87%, with most of the radioactive dose recovered from feces (approximately 86%). Unchanged ledipasvir excreted in feces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. These data indicate 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 following administration of Ledipasvir and Sofosbuvir tablet 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, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 following administration of Ledipasvir and Sofosbuvir tablet were 0.5 and 27 hours, respectively.

Specific Populations

Race: Population pharmacokinetics analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposure of ledipasvir, sofosbuvir, and GS-331007.

Gender: Population pharmacokinetics analysis in HCV-infected subjects indicated that gender had no clinically relevant effect on the exposure of sofosbuvir and 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, as high response rates (SVR12 >90%) were achieved in male and female subjects across the Phase 3 studies and the safety profiles are similar in females and males.

Pediatric Patients: The pharmacokinetics of ledipasvir or sofosbuvir in pediatric patients has not been established.

Geriatric Patients: Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 80 years) analyzed, age did not have a clinically relevant effect on the exposure to ledipasvir, sofosbuvir, and GS-331007.

Patients with Renal Impairment: The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe renal impairment (eGFR less than 30 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR between 50 to less than 80 mL/min/1.73m^2), moderate (eGFR between 30 to less than 50 mL/min/1.73m^2), severe renal impairment (eGFR less than 30 mL/min/1.73m^2), and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR greater than 80 mL/min/1.73m2), the sofosbuvir AUC_{0-inf} was 61%, 107%, and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88%, and 451% higher, respectively. In subjects with ESRD, relative to subjects with normal renal function, sofosbuvir and GS-331007 AUC_{0-inf} was 28% and 1280% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after hemodialysis, respectively. A 4 hour hemodialysis session removed approximately 18% of administered dose.

Patients with Hepatic Impairment: The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe hepatic impairment (Child-Pugh Class C). Ledipasvir plasma exposure (AUC_{0-inf}) was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of ledipasvir. The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007.

Drug Interaction Studies

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. P-gp inducers (e.g., rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations, leading to reduced therapeutic effect of Ledipasvir and Sofosbuvir tablet, and the use with P-gp inducers is not recommended with Ledipasvir and Sofosbuvir tablet. Coadministration with drugs that inhibit P-gp and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS-331007 plasma concentration; Ledipasvir and Sofosbuvir tablet may be coadministered with P-gp and/or BCRP inhibitors. Neither ledipasvir nor sofosbuvir is a substrate for hepatic uptake transporters OCT1, OATP1B1, or OATP1B3. GS-331007 is not a substrate for renal transporters, including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2.

Ledipasvir is subject to slow oxidative metabolism via an unknown mechanism. In vitro, no detectable metabolism of ledipasvir by CYP enzymes has been observed. Biliary excretion of unchanged ledipasvir is a major route of elimination. Sofosbuvir is not a substrate for CYP and UGT1A1 enzymes. Clinically significant drug interactions with Ledipasvir and Sofosbuvir tablet mediated by CYP or UGT1A1 enzymes are not expected.

The effects of coadministered drugs on the exposure of ledipasvir, sofosbuvir, and GS-331007 are shown in Table 5.

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Ledipasvir, Sofosbuvir, and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug*

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir, and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF†‡	300/100 + 200/300 once daily	90 once daily	400 once daily	24	ledipasvir	1.68 (1.54, 1.84)	1.96 (1.74, 2.21)	2.18 (1.91, 2.50)
					sofosbuvir	1.01 (0.88, 1.15)	1.11 (1.02, 1.21)	NA
					GS-331007	1.17 (1.12, 1.23)	1.31 (1.25, 1.36)	1.42 (1.34, 1.49)
Cyclosporine	600 single dose	ND	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Darunavir /ritonavir	800/100 once daily	90 once daily	ND	23	ledipasvir	1.45 (1.34, 1.56)	1.39 (1.28, 1.49)	1.39 (1.29, 1.51)
		ND	400 single dose	18	sofosbuvir	1.45 (1.10, 1.92)	1.34 (1.12, 1.59)	NA
					GS-331007	0.97 (0.90, 1.05)	1.24 (1.18, 1.30)	NA
Darunavir/ ritonavir + emtricitabine / tenofovir DF†	800/100 + 200/300 once daily	90 once daily	400 once daily	23	ledipasvir	1.11 (0.99, 1.24)	1.12 (1.00, 1.25)	1.17 (1.04, 1.31)
					sofosbuvir	0.63 (0.52, 0.75)	0.73 (0.65, 0.82)	NA
					GS-331007	1.10 (1.04, 1.16)	1.20 (1.16, 1.24)	1.26 (1.20, 1.32)
Efavirenz/ emtricitabine/ tenofovir DF§	600/200/300 once daily	90 once daily	400 once daily	14	ledipasvir	0.66 (0.59, 0.75)	0.66 (0.59, 0.75)	0.66 (0.57, 0.76)
					sofosbuvir	1.03 (0.87, 1.23)	0.94 (0.81, 1.10)	NA
					GS-331007	0.86 (0.76, 0.96)	0.90 (0.83, 0.97)	1.07 (1.02, 1.13)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	150/150/200/10 once daily	90 once daily	400 once daily	30	ledipasvir	1.65 (1.53, 1.78)	1.79 (1.64, 1.96)	1.93 (1.74, 2.15)
					sofosbuvir	1.28 (1.13, 1.47)	1.47 (1.35,1.59)	NA
					GS-331007	1.29 (1.24, 1.35)	1.48 (1.44, 1.53)	1.66 (1.60, 1.73)
Famotidine	40 single dose simultaneously with Ledipasvir and Sofosbuvir tablet	90 once daily	400 single dose	12	ledipasvir	0.80 (0.69, 0.93)	0.89 (0.76, 1.06)	NA
					sofosbuvir	1.15 (0.88, 1.50)	1.11 (1.00, 1.24)	NA
					GS-331007	1.06 (0.97, 1.14)	1.06 (1.02, 1.11)	NA
	40 single dose 12 hours prior to Ledipasvir and Sofosbuvir tablet			12	ledipasvir	0.83 (0.69, 1.00)	0.98 (0.80, 1.20)	NA
					sofosbuvir	1.00 (0.76, 1.32)	0.95 (0.82, 1.10)	NA
					GS-331007	1.13 (1.07, 1.20)	1.06 (1.01, 1.12)	NA
Methadone	30 to 130 daily	ND	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA
Omeprazole	20 once daily simultaneously with Ledipasvir and Sofosbuvir tablet	90 single dose	400 single dose	16	ledipasvir	0.89 (0.61, 1.30)	0.96 (0.66, 1.39)	NA
					sofosbuvir	1.12 (0.88, 1.42)	1.00 (0.80, 1.25)	NA
					GS-331007	1.14 (1.01, 1.29)	1.03 (0.96, 1.12)	NA
	20 once daily 2 hours prior to ledipasvir	30 single dose	ND	17	ledipasvir	0.52 (0.41, 0.66)	0.58 (0.48, 0.71)	NA
Rifampin	600 once daily	90 single dose¶	ND	31	ledipasvir	0.65 (0.56, 0.76)	0.41 (0.36, 0.48)	NA
		ND	400 single dose	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA
Simeprevir	150 once daily	30 once daily	ND	22	ledipasvir	1.81 (1.69, 2.94)	1.92 (1.77, 2.07)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available/not applicable, ND = not dosed.

tenofovir DF = tenofovir disoproxil fumarate

* All interaction studies conducted in healthy volunteers

† Data generated from simultaneous dosing with Ledipasvir and Sofosbuvir tablet Staggered administration (12 hours apart) of atazanavir/ritonavir + emtricitabine/tenofovir DF or darunavir/ritonavir + emtricitabine/tenofovir DF and Ledipasvir and Sofosbuvir tablet provided similar results.

‡ The effects of atazanavir/ritonavir on ledipasvir and sofosbuvir are similar with or without the presence of emtricitabine/ tenofovir DF.

§ Administered as ATRIPLA® (efavirenz, emtricitabine, tenofovir DF).

¶ This study was conducted in the presence of two other investigational HCV direct-acting agents.

No effect on the pharmacokinetic parameters of ledipasvir, sofosbuvir, and GS-331007 was observed with raltegravir and the combination of abacavir and lamivudine; emtricitabine, rilpivirine, and tenofovir disoproxil fumarate; or dolutegravir, emtricitabine, and tenofovir disoproxil fumarate.

Ledipasvir is an inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir is an inhibitor of transporters OATP1B1, OATP1B3, and BSEP only at concentrations exceeding those

achieved in clinic. Ledipasvir is not an inhibitor of transporters MRP2, MRP4, OCT2, OAT1, OAT3, MATE1, and OCT1. The drug-drug interaction potential of ledipasvir is primarily limited to the intestinal inhibition of P-gp and BCRP. Clinically relevant transporter inhibition by ledipasvir in the systemic circulation is not expected due to its high protein binding. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, and OCT1, and GS 331007 is not an inhibitor of OAT1, OCT2, and MATE1. Ledipasvir, sofosbuvir, and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

The effects of ledipasvir or sofosbuvir on the exposure of coadministered drugs are shown in Table 6.

Table 6 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Ledipasvir, Sofosbuvir, or Ledipasvir and Sofosbuvir tablet *

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledipasvir Dose (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered Drug PK With/Without Ledipasvir, Sofosbuvir No Effect=1.00		
					C_{max}	AUC	C_{min}
Atazanavir/ ritonavir +emtricitabine / tenofovir DF†‡§	atazanavir 300 once daily	90 once daily	400 once daily	24	1.07 (0.99, 1.14)	1.27 (1.18, 1.37)	1.63 (1.45, 1.84)
	ritonavir 100 once daily				0.86 (0.79, 0.93)	0.97 (0.89, 1.05)	1.45 (1.27, 1.64)
	tenofovir DF 300 once daily				1.47 (1.37, 1.58)	1.35 (1.29, 1.42)	1.47 (1.38, 1.57)
Darunavir/ ritonavir + emtricitabine/ tenofovir DF†§	darunavir 800 once daily	90 once daily	400 once daily	23	1.01 (0.96, 1.06)	1.04 (0.99, 1.08)	1.08 (0.98, 1.20)
	ritonavir 100 once daily				1.17 (1.01, 1.35)	1.25 (1.15, 1.36)	1.48 (1.34, 1.63)
	tenofovir DF 300 once daily				1.64 (1.54, 1.74)	1.50 (1.42, 1.59)	1.59 (1.49, 1.70)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	elvitegravir 150 once daily	90 once daily	400 once daily	30	0.98 (0.90, 1.07)	1.11 (1.02, 1.20)	1.46 (1.28, 1.66)
	cobicistat 150 once daily				1.23 (1.15, 1.32)	1.53 (1.45, 1.62)	3.25 (2.88, 3.67)
	tenofovir alafenamide 10 once daily				0.90 (0.73, 1.11)	0.86 (0.78, 0.95)	NA
Norelgestromin	norgestimate 0.180/0.215/0.25/ ethinyl estradiol 0.025 once daily	90 once daily	ND	15	1.02 (0.89, 1.16)	1.03 (0.90, 1.18)	1.09 (0.91, 1.31)
		ND	400 once daily		1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel		90 once daily	ND		1.03 (0.87, 1.23)	0.99 (0.82, 1.20)	1.00 (0.81, 1.23)
		ND	400 once daily		1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol		90 once daily	ND		1.40 (1.18, 1.66)	1.20 (1.04, 1.39)	0.98 (0.79, 1.22)
		ND	400 once daily		1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Raltegravir	400 twice daily	90 once daily	ND	28	0.82 (0.66, 1.02)	0.85 (0.70, 1.02)	1.15 (0.90, 1.46)
		ND	400 single dose	19	0.57 (0.44, 0.75)	0.73 (0.59, 0.91)	0.95 (0.81, 1.12)
Simeprevir	150 once daily	30 once daily	ND	22	2.61 (2.39, 2.86)	2.69 (2.44, 2.96)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Tenofovir DF	300 once daily¶	90 once daily	400 once daily	15	1.79 (1.56, 2.04)	1.98 (1.77, 2.23)	2.63 (2.32, 2.97)

NA = not available/not applicable, ND = not dosed.

tenofovir DF = tenofovir disoproxil fumarate

* All interaction studies conducted in healthy volunteers.

† Data generated from simultaneous dosing with Ledipasvir and Sofosbuvir tablet. Staggered administration (12 hours apart) of atazanavir/ritonavir + emtricitabine/tenofovir DF or darunavir/ritonavir+emtricitabine/tenofovir DF and Ledipasvir and Sofosbuvir tablet provided similar results.

‡ The effects of Ledipasvir and Sofosbuvir tablet on atazanavir and ritonavir are similar with or without the presence of emtricitabine/tenofovir DF.

§ This magnitude of change in tenofovir exposure does not reflect the approximately 60%–80% increase caused by the effects of an HIV PI/ritonavir and the effect of food. Therefore, tenofovir exposure is approximately 130% higher when administered as tenofovirDF + atazanavir/ritonavir + Ledipasvir and Sofosbuvir tablet or tenofovirDF + darunavir/ritonavir + Ledipasvir and Sofosbuvir tablet and with food as compared to the tenofovir exposure observed following fasted administration of tenofovir DF-based regimens that do not contain an HIV PI/ritonavir and Ledipasvir and Sofosbuvir tablet.

¶ Administered as ATRIPLA (efavirenz, emtricitabine, tenofovir DF). The effects of Ledipasvir and Sofosbuvir on tenofovir exposures are similar when tenofovir is administered as ATRIPLA, COMPLERA, or TRUVADA+dolutegravir.

Microbiology

Mechanism of Action

Ledipasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotypes 1b and 4a with IC_{50} values of 3.3 and 2.7 microM, respectively. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral Activity

In HCV replicon assays, the EC_{50} values of ledipasvir against full-length replicons from genotypes 1a and 1b were 0.031 nM and 0.004 nM, respectively. The median EC_{50} values of ledipasvir against chimeric replicons encoding NS5A sequences from clinical isolates were 0.018 nM for genotype 1a (range 0.009–0.085 nM; N=30) and 0.006 nM for genotype 1b (range 0.004–0.007 nM; N=3). Ledipasvir has less antiviral activity compared to genotype 1 against genotypes 4a, 5a, and 6a, with EC_{50} values of 0.39 nM, 0.15 nM, and 1.1 nM, respectively, and substantially lower activity against genotype 6e with an EC_{50} value of 264 nM.

In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotypes 1a, 1b, and 4a, and chimeric 1b replicons encoding NS5B from genotypes 5a or 6a ranged from 14–110 nM. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 62 nM for genotype 1a (range 29–128 nM; N=67) and 102 nM for genotype 1b (range 45–170 nM; N=29). In replication competent virus assays, the EC_{50} value of sofosbuvir against genotype 1a was 30 nM. Evaluation of sofosbuvir in combination with ledipasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to ledipasvir have been selected in cell culture for genotypes 1a and 1b. Reduced susceptibility to ledipasvir was associated with the primary NS5A amino acid substitution Y93H in both genotypes 1a and 1b. Additionally, a Q30E substitution emerged in genotype 1a replicons. Site-directed mutagenesis of the Y93H in both genotypes 1a and 1b, as well as the Q30E substitution in genotype 1a, conferred high levels of reduced susceptibility to ledipasvir (fold change in EC_{50} greater than 1000-fold).

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 4a, 5a, and 6a. Reduced susceptibility to sofosbuvir was associated with the NS5B substitution S282T in all replicon genotypes examined. An M289L substitution developed along with the S282T substitution in genotype 5 and 6 replicons. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir.

In Clinical Trials

Genotype 1

In a pooled analysis of subjects who received Ledipasvir and Sofosbuvir tablet in Phase 3 trials (ION-3, ION-1 and ION-2), 37 subjects (29 with genotype 1a HCV and 8 with genotype 1b HCV) qualified for resistance analysis due to virologic failure (35 with virologic relapse, 2 with breakthrough on-treatment due to documented non-adherence). Post-baseline NS5A and NS5B deep nucleotide sequence analysis data (assay sensitivity of 1%) were available for 37/37 and 36/37 subjects' viruses, respectively.

Of the 29 genotype 1a virologic failure subjects, 55% (16/29) of subjects had virus with emergent NS5A resistance-associated substitutions K24R, M28T/V, Q30R/H/K/L, L31M, or Y93H/N at failure. Five of these 16 subjects' viruses also had baseline NS5A polymorphisms at resistance-associated amino acid positions. The most common substitutions detected at failure were Q30R, Y93H or N, and L31M.

Of the 8 genotype 1b virologic failure subjects, 88% (7/8) had virus with emergent NS5A resistance-associated substitutions L31V/M/I or Y93H at failure. Virus from three of these 7 subjects also had baseline NS5A polymorphisms at resistance-associated positions. The most common substitution detected at failure was Y93H.

At failure, 38% (14/37) of virologic failure subjects' viruses had 2 or more NS5A substitutions at resistance-associated positions.

In the SOLAR-1 and SOLAR-2 trials (liver transplant recipients or subjects with decompensated liver disease), there were 24 virologic failures with genotype 1 infection (20 relapsers and 4 subjects who discontinued treatment prior to achieving HCV RNA <LLOQ). Treatment-emergent NS5A resistance-associated substitutions K24R, M28T, Q30R/H/K, L31V, H58D/P and/or Y93H/C were detected in 14/17 (82%) genotype 1a virologic failure subjects, and R30Q, L31M and/or Y93H/N were detected in 6/7 (86%) genotype 1b virologic failure subjects.

In phenotypic analyses, post-baseline isolates from subjects who harbored- NS5A resistance-associated substitutions at failure showed 20- to >243-fold reduced susceptibility to ledipasvir.

Treatment-emergent NS5B substitutions L159 (n=1) and V321 (n=2) previously associated with sofosbuvir failure were detected in the Phase 3 trials (ION-3, ION-1 and ION-2). In addition, treatment-emergent NS5B substitutions at highly conserved positions D61G (n=3), A112T (n=2), E237G (n=2), and S473T (n=1) were detected at low frequency by next generation sequencing in treatment failure subjects infected with HCV genotype 1a. The D61G substitution was previously described in subjects infected with HCV genotype 1a in a liver pre-transplant trial. The E237G substitution was detected in 3 subjects infected with HCV GT1a in the SOLAR-1 and SOLAR-2 trials. The clinical significance of these substitutions is currently unknown. The sofosbuvir-associated resistance substitution S282T in NS5B was not detected in any failure isolate from the Phase 3 trials. NS5B substitutions S282T, L320V/I, and V321I in combination with NS5A substitutions L31M, Y93H, and Q30L were detected in one subject at failure following 8 weeks of treatment with Ledipasvir and Sofosbuvir tablet in a phase 2 trial.

Genotype 4, 5 or 6

Resistance analysis was performed for 6 relapse subjects infected with HCV genotype 4 (Study 1119 and ION-4, N=3), genotype 5 (Study 1119, N=2) or genotype 6 (ELECTRON-2; N=1) and treated with Ledipasvir and Sofosbuvir tablet for 12 weeks. All the relapse subjects with NS5A sequencing data (5 of 6) had pretreatment NS5A resistance-associated polymorphisms (single or combinations at positions 24, 28, 30, 31 and 58). NS5A resistance substitutions (Y93C or L28V) emerged in two of the genotype 4 relapse subjects post-treatment who also had NS5A polymorphisms pretreatment that were retained post-treatment. Two of the relapsers with genotype 4 HCV infection had an NS5B V321I substitution pretreatment, which was retained post-treatment. Three of the relapse subjects (1 each for genotype 4, 5, and 6) had virus with emergent sofosbuvir resistance-associated substitution S282T at relapse; the genotype 5 relapse subject also had emergent nucleotide inhibitor substitution M289I.

Effect of Baseline HCV Polymorphisms on Treatment Response

Genotype 1

Analyses were conducted to explore the association between pre-existing baseline NS5A polymorphisms at resistance-associated positions and relapse rates. In the pooled analysis of the Phase 3 trials, 23% (370/1589) of subjects' virus had baseline NS5A polymorphisms at resistance-associated positions (any change from reference at NS5A amino acid positions 24, 28, 30, 31, 58, 92, or 93) identified by population or analysis of deep nucleotide sequences with a 15% frequency threshold.

In treatment-naïve subjects whose virus had baseline NS5A polymorphisms at resistance-associated positions in Studies ION-1 and ION-3, relapse rates were 6% (3/48) after 8 weeks and 1% (1/113) after 12 weeks of treatment with Ledipasvir and Sofosbuvir tablet. Relapse rates among subjects without baseline NS5A polymorphisms at resistance-associated positions were 5% (8/167) after 8 weeks and 1% (3/306) after 12 weeks treatment with Ledipasvir and Sofosbuvir tablet.

In treatment-experienced subjects in Study ION-2 whose virus had baseline NS5A polymorphisms at resistance-associated positions, relapse rates were 22% (5/23) after 12 weeks and 0% (0/19) after 24 weeks of treatment with Ledipasvir and Sofosbuvir tablet. In another study in treatment-experienced subjects (SIRIUS), 0/15 (0%) subjects with NS5A polymorphisms at resistance-associated positions relapsed after 12 weeks of treatment with Ledipasvir and Sofosbuvir tablet +RBV compared to 2/15 (13%) subjects treated with 24 weeks of Ledipasvir and Sofosbuvir tablet.

SVR was achieved in all 24 subjects (N=20 with L159F+C316N; N=1 with L159F; and N=3 with N142T) who had baseline polymorphisms associated with resistance to sofosbuvir and/or other NS5B nucleoside inhibitors. The NS5B S282T substitution associated with resistance to sofosbuvir was not detected in the baseline NS5B sequence of any subject in Phase 3 trials by population or deep nucleotide sequence analysis.

In the SOLAR-1 and SOLAR-2 trials (liver transplant recipients or subjects with decompensated liver disease), after 12 weeks of treatment with Ledipasvir and Sofosbuvir tablet + RBV, relapse rates were 7% (5/71) and 5% (10/217) in genotype 1 subjects with and without baseline NS5A polymorphisms at resistance-associated positions, respectively.

In the Phase 3 trials and SOLAR trials, the specific baseline NS5A resistance-associated polymorphisms observed among subjects who relapsed were M28T/V, Q30H/R, L31M, H58D/P, and Y93H/N in genotype 1a, and L28M, L31M, A92T, and Y93H in genotype 1b. Subjects with multiple NS5A polymorphisms at resistance-associated positions appeared to have higher relapse rates.

Genotype 4, 5 or 6

Phylogenetic analysis of HCV sequences from genotype 4-infected subjects in Study 1119 (N=44) and ION-4 (N=8) identified 7 HCV genotype 4 subtypes (4a, 4b, 4d, 4f, 4m, 4o and 4r). Most subjects were infected with subtype 4a (N=32; 62%) or 4d (N=11; 21%); 1 to 3 subjects were infected with each of the other genotype 4 subtypes. There were 3 subjects with subtype 4r, 2 of whom experienced virologic relapse, and both had a combination of 2 pretreatment NS5A resistance-associated polymorphisms (L28M/V+L30R).

Phylogenetic analysis of HCV sequences from genotype 5-infected subjects in Study 1119 showed almost all were subtype 5a (N=39) with one subject not having a subtype identified at screening or by analysis.

Phylogenetic analysis of HCV sequences from genotype 6-infected subjects in ELECTRON-2 identified 7 HCV genotype 6 subtypes (6a, 6e, 6l, 6m, 6p, 6q and 6r). Thirty-two percent of the subjects had subtype 6a and 24% had subtype 6e. One to three subjects were infected with the other subtypes 6l, 6m, 6p, 6q, or 6r. The one subject who did not achieve SVR12 had subtype 6l.

Although the data are limited, baseline HCV NS5A resistance-associated polymorphisms are not expected to impact the likelihood of achieving SVR when Ledipasvir and Sofosbuvir tablet is used as recommended to treat HCV genotype 4, 5, or 6-infected patients, based on the low virologic failure rate observed in Study 1119 and ELECTRON-2. The specific baseline polymorphisms observed in subjects with virologic failure were L28M/V, L30R, and P58T for genotype 4; L31M for genotype 5; and Q24K, F28V, R30A and T58P for genotype 6.

Relapse occurred in 2 of 3 genotype 4 subjects who had baseline NS5B V321I, a polymorphism at a position associated with treatment failure to sofosbuvir and other nucleoside inhibitors; these two subjects also had baseline NS5A resistance-associated polymorphisms. For genotype 5 and 6, SVR12 was achieved in subjects who had baseline NS5B polymorphisms at positions associated with resistance to sofosbuvir and other nucleoside inhibitors (N=1 with N142T in genotype 5; N=1 with M289I in genotype 5; N=15 with M289L/I in genotype 6). The sofosbuvir resistance-associated substitution S282T was not detected in the baseline NS5B sequence of any subject with genotype 4, 5 or 6 HCV in clinical trials by population or deep nucleotide sequence analysis.

Cross Resistance

Based on resistance patterns observed in cell culture replicon studies and HCV-infected subjects, cross-resistance between ledipasvir and other NS5A inhibitors is expected. Both sofosbuvir and ledipasvir were fully active against substitutions associated with resistance to other classes of direct-acting antivirals with different mechanisms of action, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. The efficacy of ledipasvir/sofosbuvir has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

HOW SUPPLIED/STORAGE AND HANDLING

Brown, Capsule shape, bevel edged biconvex, film-coated tablets debossed with 'H' on one side and 'L 18' on other side.

Storage Condition: Store at temperatures not exceeding 30°C. Protect from moisture

Container pack : White Opaque HDPE bottle (Box of 28 Tablets)

Lisof is manufactured under a license from Gilead Sciences Ireland

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR REPORTING STATEMENT: For suspected adverse drug reaction. report to the FDA: www.fda.gov.ph

REFERENCE: 1. HARVONI® (Ledipasvir and sofosbuvir) tablets USFDA prescribing Information leaflet

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