Sofoveravir

Film coated tablet

Sofosbuvir 400 mg

Ledipasvir 90 mg

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

Therapeutic indications

Sofoveravir is indicated for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to < 18 years.

For hepatitis C virus (HCV) genotype-specific activity see special warnings and precautions and pharmacodynamics properties.

Posology and method of administration

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

Posology

Adults and adolescents aged 12 to < 18 years
The recommended dose sofoveravir is one tablet once daily with or without food

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

Patient population (including HIV co-infected patients)	**Treatment and duration**
Adult and Adolescent patients 12 years of age or older with genotype 1, 4, 5 or 6 CHC	
Patients without cirrhosis	Sofoveravir for 12 weeks. sofoveravir for 8 weeks may be considered in previously untreated genotype 1-infected patients
Patients with compensated cirrhosis	Sofoveravir + ribavirin[A] for 12 weeks Or sofoveravir (without ribavirin) for 24 weeks.

	-sofoveravir (without ribavirin) for 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options
Patients who are post-liver transplant without cirrhosis or with compensated cirrhosis	Sofoveravir + ribavirin[A] for 12 weeks - sofoveravir (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	Sofoveravir + ribavirin[B] for 12 weeks sofoveravir (without ribavirin) for 24 weeks may be considered in patients who are ineligible for or intolerant to ribavirin.
Adult and Adolescent patients 12 years of age or older with genotype 3 CHC	
Patients with compensated cirrhosis and/or prior treatment failure	Sofoveravir + ribavirin[A] for 24 weeks

[A]Adults: weight based ribavirin (< 75 kg = 1,000 mg and ≥ 75 kg = 1,200 mg), administered orally in two divided doses with food. Adolescents: for ribavirin dosing recommendations see table 3 below.
[B] For ribavirin dosing recommendations in patients with decompensated cirrhosis, see table 2 below

Table 2: Guidance for ribavirin dosing when administered with sofoveravir 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 fo those weighing ≥ 75 kg
CPT Class C cirrhosis pre-transplant CPT Class B or C cirrhosis post-transplant	Starting dose of 600 mg, which can be titrated up to a maximum of 1,000/1,200 mg (1,000 mg for patients weighing < 75 kg and 1,200 mg for patients weighing ≥ 75 kg) if well tolerated. If the starting dose is not well tolerated, the dose should be reduced as clinically indicated based on haemoglobin levels

* - If a more normalized dose of ribavirin (by weight and renal function) cannot be reached for reasons of tolerability, 24 weeks of sofoveravir + ribavirin should be considered in order to minimize the risk for relapse.
When ribavirin is added to sofoveravir, refer also to the Summary of Product Characteristics of ribavirin.

In adolescent patients aged 12 to <18 years the following ribavirin dosing is recommended where ribavirin is divided into two daily doses and given with food:

Table 3. Guidance for ribavirin dosing when administered with sofoveravir to adolescents aged 12 to < 18 years.

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

* Ribavirin administered orally in two divided doses with food.
Dose modification of ribavirin in adults taking 1,000-1,200 mg daily

If sofoveravir is used in combination with ribavirin and a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 4 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status

Table 4: Ribavirin dose modification guideline for co-administration with sofoveravir in adults

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

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

Paediatric Population aged <12 years

The safety and effectiveness of sofosbuvir / ledipasvir in paediatric patients aged < 12 years have not been established. No data on paediatric patients aged < 12 years are available.

Missed dose

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

Renal impairment

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

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

Method of administration

For oral use.
Patients should be instructed to swallow the tablet whole with or without food. Due to the bitter taste, it is recommended that the film-coated tablet is not chewed or crushed

Contraindications
Hypersensitivity to the active substances or to any of the excipients
Co-administration with rosuvastatin

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

Special warnings and precautions for use
Sofoveravir should not be administered concomitantly with other medicinal products containing sofosbuvir.

Genotype-specific activity

Concerning recommended regimens with different HCV genotypes. Concerning genotype-specific virological and clinical activity

The clinical data to support the use of sofosbuvir / ledipasvir in adults infected with HCV genotype 3 are limited .The relative efficacy of a 12-week regimen consisting of ledipasvir/sofosbuvir + ribavirin, compared to a 24-week regimen of sofosbuvir + ribavirin has not been investigated. A conservative 24 weeks of therapy is advised in all treatment-experienced genotype 3 patients and those treatment-naïve genotype 3 patients with cirrhosis. In genotype 3-infection, the use of sofoveravir (always in combination with ribavirin) should only be considered for patients who are deemed at high risk for clinical disease progression and who do not have alternative treatment options.

The clinical data to support the use of sofosbuvir / ledipasvir in adults infected with HCV genotype 2 and 6 are limited .

Serious Symptomatic Bradycardia When Coadministered with Amiodarone and Another HCV Direct Acting Antiviral

Post marketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with Sofosbuvir in combination with an investigational agent (NS5A inhibitor) or simeprevir. A fatal cardiac arrest was reported in a patient receiving a sofosbuvir-containing regimen (ledipasvir/sofosbuvir)). 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 Sofosbuvir in combination with another direct acting antiviral (DAA) is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered Sofosbuvir and another DAA :

• 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 Sofosbuvir in combination with another DAA who need to start amiodarone therapy due to no other alternative, viable treatment options should 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

Severe bradycardia and heart block

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

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

Should concomitant use of amiodarone be considered necessary it is recommended that patients are closely monitored when initiating sofoveravir Patients who are identified as being high risk of bradyarrhythmia should be continuously monitored for 48 hours in an appropriate clinical setting.
Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofoveravir
All patients receiving sofoveravir in combination with amiodarone with or without other drugs that lower heart rate should also be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

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

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

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 sofoveravir 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 sofoveravir . co-dministration of such medicinal products is not recommended with sofoveravir

Use with certain HIV antiretroviral regimens
Sofoveravir 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 sofosbuvir / ledipasvir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration sofoveravir 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 sofoveravir 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 sofoveravir and HMG-CoA reductase inhibitors (statins) can significantly increase the concentration of the statin, which increases the risk of myopathy and rhabdomyolysis

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

Paediatric population
sofosbuvir / ledipasvir is not recommended for use in paediatric patients aged < 12 years because the safety and efficacy have not been established in this population

Interaction with other medicinal products and other forms of interaction

Coadministration of amiodarone with Sofosbuvir in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unk nown.
Coadministration of amiodarone with Sofosbuvir in combination with another DAA is not recommended; if coadministration is required, cardiac monitoring is recommended

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

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

Potential for other medicinal products to affect sofoveravir
Ledipasvir and sofosbuvir are substrates of drug transporter P-gp and BCRP while GS-331007 is not. Medicinal products that are potent P-gp inducers (rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may significantly decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of ledipasvir/sofosbuvir and thus are contraindicated with sofoveravir. 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 sofoveravir Co-administration with such medicinal products is not

recommended with sofoveravir. 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; sofoveravir 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 sofoveravir a close monitoring of International Normalised Ratio (INR) values is recommended.

Interactions between sofoveravir and other medicinal products

Table 5 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 5: Interactions between sofoveravir and other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}[a, b]**	**Recommendation concerning co-administration with sofoveravir**
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 sofoveravir 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	Ledipasvir ↓ C_{max} 0.80 (0.69, 0.93) ↔ AUC 0.89 (0.76, 1.06)	H_2-receptor antagonists may be administered simultaneously with or staggered from sofoveravir at a dose that does not exceed doses comparable to famotidine 40 mg

simultaneously with sofoveravir[d] Cimetidine[e] Nizatidine[e] Ranitidine[e]	Sofosbuvir C_{max} 1.15 (0.88, 1.50) ↔ AUC 1.11 (1.00, 1.24) GS-331007 ↔ C_{max} 1.06 (0.97, ↔ AUC 1.06 (1.02, 1.11) (Increase in gastric pH)	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 sofoveravir[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 sofoveravir 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 sofoveravir. Proton pump inhibitors should not be taken before sofoveravir.
ANTIARRHYTHMICS		
Amiodarone	Interaction not studied.	Use only if no other alternative is available. Close monitoring is recommended if this medicinal product is administered with sofoveravir. Patients who are taking Sofosbuvir in combination with another DAA 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 Sofosbuvir in combination with a DAA should also undergo similar cardiac monitoring as outlined above.
Digoxin	Interaction not studied. Expected: ↑ Digoxin ↔ Ledipasvir ↔ Sofosbuvir ↔ GS-331007 (Inhibition of P-gp)	Co-administration sofoveravir with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with sofoveravir
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 sofoveravir . 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 sofoveravir
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Interaction not studied. Expected: ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Sofoveravir is contraindicated with carbamazepine, phenobarbital and phenytoin, potent intestinal P-gp inducers
Oxcarbazepine	Interaction not studied. Expected: ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of sofoveravir with oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir leading to reduced therapeutic effect of sofoveravir Such co-administration is not recommended
ANTIMYCOBACTERIALS		
Rifampicin (600 mg once daily)/ ledipasvir (90 mg single dose)[d]	Interaction not studied. Expected: Rifampicin	Sofoveravir is contraindicated with rifampicin, a potent intestinal P-gp inducer

	↔ 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)	
Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d]	Interaction not studied. Expected: Rifampicin ↔ C_{max} ↔ AUC ↔ C_{min} Observed: Sofosbuvir ↓ C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) GS-331007 ↔ C_{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) (Induction of P-gp)	
Rifabutin Rifapentine	Interaction not studied. Expected: ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Sofoveravir is contraindicated with rifabutin, a potent intestinal P-gp inducer Co-administration of sofoveravir with rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect sofoveravir . Such co-administration is not recommended.
HCV PRODUCTS		
Simeprevir (150 mg once daily)/ ledipasvir (30 mg once daily)	Simeprevir ↑ C_{max} 2.61 (2.39, 2.86) ↑ AUC 2.69 (2.44, 2.96) Ledipasvir ↑ C_{max} 1.81 (1.69, 2.94) ↑ AUC 1.92 (1.77, 2.07)	Concentrations of ledipasvir, sofosbuvir and simeprevir are increased when simeprevir is co-administered with sofoveravir Co-administration is not recommended.
Simeprevir[h]	Simeprevir ↔ C_{max} 0.96 (0.71, 1.30)	

	↔ AUC 0.94 (0.67, 1.33) Sofosbuvir ↑ C_{max} 1.91 (1.26, 2.90) ↑ AUC 3.16 (2.25, 4.44) GS-331007 ↓ C_{max} 0.69 (0.52, 0.93) ↔ AUC 1.09 (0.87, 1.37)	
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 sofoveravir or efavirenz/ emtricitabine/ tenofovir disoproxil fumarate is required.
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate	Emtricitabine ↔ C_{max} 1.02 (0.98, 1.06)	No dose adjustment of sofoveravir or emtricitabine/ rilpivirine/ tenofovir

(200 mg/ 25 mg/ 300 mg once daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]	↔ 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)	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 sofoveravir or abacavir/ lamivudine is required.
HIV ANTIVIRAL AGENTS: HIV PROTEASE INHIBITORS		
Atazanavir boosted with ritonavir (300 mg/ 100 mg once	Atazanavir ↔ C_{max} 1.07 (1.00,	No dose adjustment of sofoveravir or atazanavir (ritonavir boosted) is

daily)/ ledipasvir (90 mg once daily)[c]/ sofosbuvir (400 mg once daily)[c, d]	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)	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	When given with tenofovir disoproxil fumarate used in conjunction with atazanavir/ritonavir, sofoveravir increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of sofoveravir 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 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.

	↔ C_{max} 1.17 (1.12, 1.23) ↔ AUC 1.31 (1.25, 1.36) ↑ C_{min} 1.42 (1.34, 1.49)	
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 sofoveravir 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,	When given with darunavir/ritonavir used in conjunction with tenofovir disoproxil fumarate, sofoveravir increased the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of sofoveravir 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

	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)	
Lopinavir boosted with ritonavir + emtricitabine/ tenofovir disoproxil fumarate	Interaction not studied. Expected: ↑ Lopinavir ↑ Ritonavir ↔ Emtricitabine ↑ Tenofovir ↑ Ledipasvir ↔ Sofosbuvir ↔ GS-331007	When given with lopinavir/ritonavir used in conjunction with tenofovir disoproxil fumarate, Harvoni is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of sofoveravir 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
Tipranavir boosted with ritonavir	Interaction not studied. Expected: ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	Co-administration of sofoveravir with tipranavir (ritonavir boosted) is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect sofoveravir . 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 sofoveravir 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)	When given with elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate, sofoveravir i is expected to increase the concentration of tenofovir. The safety of tenofovir disoproxil fumarate in the setting of sofoveravir 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

	↑ 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)	
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)	Sofoveravir is contraindicated with St. John's wort, a potent intestinal P-gp inducer
HMG-CoA REDUCTASE INHIBITORS		
Rosuvastatin[g]	↑ Rosuvastatin (Inhibition of drug transporters OATP and BCRP)	Co-administration of sofoveravir 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 sofoveravir with rosuvastatin is contraindicated
Pravastatin[g]	↑ Pravastatin	Co-administration of Harvoni with pravastatin may significantly increase the concentration of pravastatin which is associated with increased risk of myopathy. Clinical and biochemical control is recommended in these patients and a dose adjustment may be needed
Other statins	Expected: ↑ Statins	Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with sofoveravir a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken
NARCOTIC ANALGESICS		

Methadone	Interaction not studied. Expected: ↔ Ledipasvir	No dose adjustment of sofoveravir 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 sofoveravir or ciclosporin is 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 sofoveravir or tacrolimus is required.
Tacrolimus (5 mg single dose)/ sofosbuvir (400 mg single dose)[h]	Tacrolimus ↓ C_{max} 0.73 (0.59, 0.90) ↑ AUC 1.09 (0.84, 1.40) Sofosbuvir ↓ C_{max} 0.97 (0.65, 1.43)	

	↑ AUC 1.13 (0.81, 1.57) GS-331007 ↔ C_{max} 0.97 (0.83, 1.14) ↔ AUC 1.00 (0.87, 1.13)	
ORAL CONTRACEPTIVES		
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ ledipasvir (90 mg once daily)[d]	Norelgestromin ↔ C_{max} 1.02 (0.89, 1.16) ↔ AUC 1.03 (0.90, 1.18) ↔ C_{min} 1.09 (0.91, 1.31) Norgestrel ↔ C_{max} 1.03 (0.87, 1.23) ↔ AUC 0.99 (0.82, 1.20) ↔ C_{min} 1.00 (0.81, 1.23) Ethinyl estradiol ↑ C_{max} 1.40 (1.18, 1.66) ↔ AUC 1.20 (1.04, 1.39) ↔ C_{min} 0.98 (0.79, 1.22)	No dose adjustment of oral contraceptives is required.
Norgestimate/ ethinyl estradiol (norgestimate 0.180 mg/ 0.215 mg/ 0.25 mg/ ethinyl estradiol 0.025 mg)/ sofosbuvir (400 mg once daily)[d]	Norelgestromin ↔ C_{max} 1.07 (0.94, 1.22) ↔ AUC 1.06 (0.92, 1.21) ↔ C_{min} 1.07 (0.89, 1.28) Norgestrel ↔ C_{max} 1.18 (0.99, 1.41) ↑ AUC 1.19 (0.98, 1.45) ↑ C_{min} 1.23 (1.00, 1.51) Ethinyl estradiol ↔ C_{max} 1.15 (0.97, 1.36) ↔ AUC 1.09 (0.94, 1.26) ↔ C_{min} 0.99 (0.80, 1.23)	

a. Mean ratio (90% CI) of co-administered drug pharmacokinetics of study medicinal products alone or in combination. No effect = 1.00.
b. All interaction studies conducted in healthy volunteers.
c. Administered as sofosbuvir / ledipasvir.
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 sofosbuvir / ledipasvir provided similar results.
g. This study was conducted in the presence of another two direct-acting antiviral agents.
h. Bioequivalence/Equivalence boundary 80-125%

Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

When sofoveravir 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 sofoveravir in pregnant women.
As a precautionary measure, it is preferable to avoid the use of sofoveravir during pregnancy.

Breast-feeding

It is unknown whether ledipasvir or sofosbuvir and its metabolites are excreted in human milk.
A risk to the newborns/infants cannot be excluded. Therefore, sofoveravir should not be used during breast-feeding.

Fertility

No human data on the effect of sofoveravir on fertility are available.
If ribavirin is co-administered with sofoveravir , the contraindications regarding use of ribavirin during pregnancy and breast-feeding apply (see also the Summary of Product Characteristics for ribavirin).

Effects on ability to drive and use machines

Sofoveravir (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.

Undesirable effects

Summary of the safety profile in adults

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.

The following adverse drug reactions have been identified with ledipasvir/sofosbuvir (Table 6). 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 6: Adverse drug reactions identified with sofosbubir / ledipasvir

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

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

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.

Paediatric population

The adverse reactions observed in adolescents aged 12 to < 18 years were consistent with those observed in clinical studies of ledipasvir/sofosbuvir in adults

Description of selected adverse reactions

Cardiac arrhythmias

Cases of severe bradycardia and heart block have been observed when sofosbuvir / ledipasvir is used with concomitant amiodarone and/or other drugs that lower heart rate

Reporting of suspected adverse reactions

reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

E-mail:

avs@averroespharma.net

regi@averroes-eg.com

info@averroes-eg.com

Or on the following address:

Block No 6048 , 6th industrial zone sadat city , Egypt. Tel: 0482630201/2

55 Hafez badawy sreet Nasr city , Egypt.

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)

21 Abd El Aziz Al Soud Street. El-Manial , Cairo , Egypt.

E-mail: pv.center@eda.mohp.gov.eg

Fax Number: +2 02 23684194

Telephone: +2 02 (23648046 , 23640368 , 23684381 , 23684288) , Extension No. 1303

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 sofoveravir If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with sofoveravir 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%.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral.

Mechanism of action

Ledipasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. Biochemical confirmation of NS5A inhibition by

ledipasvir is not currently possible as NS5A has no enzymatic function. In vitro resistance selection and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.
Sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity

The EC_{50} values of ledipasvir and sofosbuvir against full-length or chimeric replicons encoding NS5A and NS5B sequences from clinical isolates are detailed in Table 7. 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 7: 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.

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.

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.

Effects of food

Relative to fasting conditions, the administration of a single dose of ledipasvir/sofosbuvir with a moderate fat or high fat meal increased the sofosbuvir $AUC_{0\text{-}inf}$ 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. Sofoveravir 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.

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.

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

Pharmacokinetics in special populations

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

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

Renal impairment
The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault, median [range] CrCl 22 [17-29] mL/min). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment.
The pharmacokinetics of sofosbuvir were studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73 m^2), moderate (eGFR ≥ 30 and < 50 mL/min/1.73 m^2), severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and patients with ESRD requiring haemodialysis following a single 400 mg dose of sofosbuvir.

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

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

Paediatric population
Ledipasvir, sofosbuvir, and GS-331007 exposures in adolescents aged 12 to < 18 years were similar to those in adults from Phase 2/3 studies, following administration of ledipasvir/sofosbuvir (90

mg/400 mg). The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 have not been established in paediatric patients aged < 12 years

Pharmaceutical particulars

Sofosbuvir / ledipasvir, Croscarmellose sodium, Lactose spray dried, microcrystalline cellulose,

Hydrophobic colloidal silica, Talc, Magnesium stearate, Hypromellose, Polyethelene glycol, Titanium dioxide and Sunset yellow.

Special precautions for storage

Store at temperature not exceeding 30 ° C, in dry place

Nature and contents of container

Carton box printed with product information contains white HPDE bottle continuous thread child resistant polypropylene screw cap with an induction sealed, aluminium – faced liner containing 28 film coated tablets with silica gel pack and insert leaflet.

Produced by Averroes Pharma for pharmaceutical industries

Block No. 6048 6th industrial zone, Sadat city, Egypt.