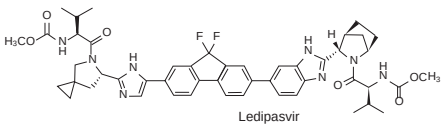
Syneget-LS™

سینِیگیٹ-ایل ایس

[Ledipasvir + Sofosbuvir]

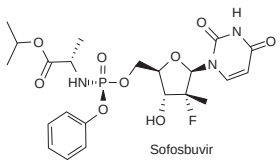
Tablets 90mg + 400mg

DESCRIPTION
Syneget-LS (Ledipasvir + Sofosbuvir) is a fixed dose combination tablet containing Ledipasvir & Sofosbuvir for oral administration which are direct-acting antiviral agents against the hepatitis C virus. Ledipasvir is an HCV NS5A inhibitor. Chemically, it 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-3-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. Its molecular formula is $C_{49}H_{54}F_2N_8O_6$ and the structural formula is:



Ledipasvir

Sofosbuvir is a nucleotide inhibitor of HCV NS5B RNA-dependent RNA polymerase. Chemically, 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. Its molecular formula is $C_{22}H_{29}FN_3O_9P$ and the structural formula is:



Sofosbuvir

QUALITATIVE & QUANTITATIVE COMPOSITION
Syneget-LS (Ledipasvir + Sofosbuvir) is available for oral administration as:

Syneget-LS Tablets 90mg + 400mg
Each film-coated tablet contains:
Ledipasvir… 90mg
Sofosbuvir… 400mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Ledipasvir
Ledipasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. Resistance selection in cell culture and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir
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.

Pharmacokinetics
Absorption
Following oral administration of ledipasvir & sofosbuvir to HCV-infected patients, 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. Ledipasvir AUC is dose proportional over the dose range of 3 to 100mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200mg to 1200mg.

Effect of Food
Relative to fasting conditions, the administration of a single dose of ledipasvir & sofosbuvir with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal increased sofosbuvir $AUC_{0\text{-inf}}$ 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. It can be administered without regard to food.

Distribution
Ledipasvir is greater than 99.8% bound to human plasma proteins. After a single 90mg 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 1µg/mL to 20µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400mg 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 90mg [^{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 400mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately greater than 90% of total systemic exposure.

Excretion
Following a single 90mg 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 is 47 hours.
Following a single 400mg 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 is 0.5 and 27 hours, respectively.

Special Population
Patients with Renal Impairment
No clinically relevant difference in ledipasvir pharmacokinetics has been observed between healthy subjects and subjects with severe renal impairment.
The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild, moderate, severe renal impairment and subjects with ESRD requiring hemodialysis following a single 400mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR greater than 80mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-inf}}$ was 61%, 107%, and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 $AUC_{0\text{-inf}}$ was 55%, 88%, and 451% higher, respectively. Sofosbuvir $AUC_{0\text{-inf}}$ was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when sofosbuvir was dosed 1 hour after hemodialysis.

Patients with Hepatic Impairment
Ledipasvir plasma exposure ($AUC_{0\text{-inf}}$) was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. Relative to subjects with normal hepatic function, the sofosbuvir $AUC_{0\text{-}24}$ were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ were 18% and 9% higher, respectively.

THERAPEUTIC INDICATIONS
Syneget-LS (Ledipasvir + Sofosbuvir) is indicated for the treatment of Chronic Hepatitis C (CHC) in adults.

DOSAGE AND ADMINISTRATION
The recommended dosage of Syneget-LS (Ledipasvir + Sofosbuvir) is one tablet taken orally once daily with or without food.

Recommended treatment duration of Syneget-LS (Ledipasvir + Sofosbuvir) and the recommended use of co-administered ribavirin for certain subgroups

Patient Population*	Treatment & Duration
Patients with genotype 1,4,5 or 6 Chronic Hepatitis C	
Patients without cirrhosis	Syneget-LS for 12 weeks - Syneget-LS for 8 weeks may be considered in previously untreated genotype 1-infected patients - Syneget-LS + ribavirin for 12 weeks or Syneget-LS (without ribavirin) for 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options
Patients with compensated cirrhosis	Syneget-LS + ribavirin for 12 weeks or Syneget-LS (without ribavirin) for 24 weeks - Syneget-LS (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	Syneget-LS + ribavirin for 12 weeks - Syneget-LS (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	Syneget-LS + ribavirin for 12 weeks - Syneget-LS (without ribavirin) for 24 weeks may be considered in patients who are ineligible for or intolerant to ribavirin
Patients with genotype 3 Chronic Hepatitis C	
Patients with compensated cirrhosis and/or prior treatment failure	Syneget-LS + ribavirin for 24 weeks

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

In patients without decompensated cirrhosis requiring the addition of ribavirin to their treatment regimen (see above Table), the daily dose of ribavirin is weight based (<75kg = 1000mg and •75kg = 1200mg) and administered orally in two divided doses with food.
In patients with decompensated cirrhosis, ribavirin should be administered at a starting dose of 600mg given in a divided daily dose. If the starting dose is well-tolerated, the dose can be titrated up to a maximum of 1000-1200mg daily (1000mg for patients weighing <75 kg and 1200mg for patients weighing •75 kg). If the starting dose is not well-tolerated, the dose should be reduced as clinically indicated based on hemoglobin levels.

Dose modification of ribavirin in patients taking 1000-1200mg daily
If Syneget-LS (Ledipasvir + Sofosbuvir) 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. Refer to the table below for dose modifications & discontinuation based on the patient's hemoglobin concentration and cardiac status:

Laboratory values	Reduce ribavirin dose to 600mg/day if:	Discontinue ribavirin if:
Hemoglobin in patients with no cardiac disease	< 10g/dL	< 8.5g/dL
Hemoglobin in patients with history of stable cardiac disease	• 2g/dL decrease in hemoglobin during any 4-week treatment period	< 12g/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 600mg daily and further increase the dose to 800mg daily. However, it is not recommended that ribavirin be increased to the originally assigned dose (1000mg to 1200mg daily).

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

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.

Special Population
Renal impairment
No dose adjustment of Syneget-LS (Ledipasvir + Sofosbuvir) is required for patients with mild or moderate renal impairment. The safety of Syneget-LS (Ledipasvir + Sofosbuvir) has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring hemodialysis.

Hepatic impairment
No dose adjustment of Syneget-LS (Ledipasvir + Sofosbuvir) is required for patients with mild, moderate or severe hepatic impairment.

Pediatric Population
The safety and efficacy of Syneget-LS (Ledipasvir + Sofosbuvir) in children and adolescents aged less than 18 years have not yet been established.

ADVERSE REACTIONS
The most common adverse reactions observed during treatment with ledipasvir + sofosbuvir are fatigue, headache and asthenia.

CONTRAINDICATIONS
Ledipasvir + sofosbuvir is contraindicated in:
- Patients with known hypersensitivity to ledipasvir or sofosbuvir or to any of the excipient of the product.
- Co-administration with rosuvastatin.
- 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.

PRECAUTIONS
- Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with ledipasvir + sofosbuvir is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended.
- The use with other drugs containing sofosbuvir is not recommended.
- If ledipasvir + sofosbuvir is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen.

Effects on ability to drive and use machines
Ledipasvir + sofosbuvir (administered alone or in combination with ribavirin) has no or negligible influence on the ability to drive and use machines. Patients should be cautioned about the risk of an influence on their ability to drive a car and operate machinery.

Pregnancy
When ledipasvir + sofosbuvir is used in combination with ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. 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. It is preferable to avoid the use of ledipasvir + sofosbuvir during pregnancy.

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

DRUG INTERACTIONS
Potential for ledipasvir + sofosbuvir 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 metabolizing 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 metabolized by these isoenzymes should be used with caution and carefully monitored.

Interactions between ledipasvir + sofosbuvir and other medicinal products

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 & magnesium hydroxide)		It is recommended to separate antacid and ledipasvir + sofosbuvir administration by 4 hours.
H_2-receptor antagonists (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir + sofosbuvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily.
Proton-pump inhibitors (e.g., omeprazole)		Proton-pump inhibitor doses comparable to omeprazole 20mg or lower can be administered simultaneously with ledipasvir + sofosbuvir under fasted conditions.
Antiarrhythmics: digoxin	↑ digoxin	Coadministration of ledipasvir + sofosbuvir with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended when coadministered with ledipasvir + sofosbuvir.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir	Coadministration of ledipasvir + sofosbuvir with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir + sofosbuvir. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin rifapentine	↓ ledipasvir ↓ sofosbuvir	Coadministration of Ledipasvir + sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir + sofosbuvir. Coadministration is not recommended. Coadministration of ledipasvir + sofosbuvir with rifampin, a P-gp inducer, is not recommended.
HIV Antiretrovirals:		
Regimens containing Tenofovir Disoproxil Fumarate without a HIV protease inhibitor	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving ledipasvir + sofosbuvir concomitantly with a regimen containing tenofovir disoproxil fumarate without a HIV protease inhibitor/ritonavir or cobicistat.
Regimens containing Tenofovir disoproxil fumarate and a HIV protease inhibitor / ritonavir or cobicistat - atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir disoproxil fumarate - darunavir/ritonavir or cobicistat + emtricitabine/tenofovir disoproxil fumarate - lopinavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of ledipasvir + sofosbuvir and 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 disoproxil fumarate	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of ledipasvir + sofosbuvir and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate has not been established. Coadministration is not recommended.
tipranavir / ritonavir	↓ ledipasvir ↓ sofosbuvir	Coadministration of ledipasvir + sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir + sofosbuvir. 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 + sofosbuvir with simeprevir is not recommended.
Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ ledipasvir ↓ sofosbuvir	Coadministration of ledipasvir + sofosbuvir with St. John's wort, a P-gp inducer is not recommended.
HMG-CoA Reductase Inhibitors: Pravastatin Other statins	↑ pravastatin ↑ statins	Co- administration of ledipasvir + sofosbuvir 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. Interactions cannot be excluded with other HMG-CoA reductase inhibitors. When co-administered with ledipasvir + sofosbuvir, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken.
Anticoagulants: Dabigatran etexilate	↑ dabigatran	Clinical monitoring, looking for signs of bleeding and anemia, is recommended when dabigatran etexilate is co-administered with ledipasvir + sofosbuvir. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

OVERDOSAGE
The highest documented doses of ledipasvir and sofosbuvir were 120mg twice daily for 10 days and a single dose of 1200mg, respectively. 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.
No specific antidote is available for overdose. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with ledipasvir + sofosbuvir 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 as 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%.

STORAGE
Store below 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Syneget-LS (Ledipasvir + Sofosbuvir) Tablets 90mg + 400mg are available in pack of 28's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
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