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 Matrix (5R,11R)-5-(((4S,5S)-5-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. Its molecular formula is C_{38}H_{31}FNO_{10}P and the structural formula is:

![Ledipasvir structure]

Sofosbuvir is a nucleoside inhibitor of HCV NS5B RNA-dependent RNA polymerase. Chemically, sofosbuvir is (S)-3-(5-isopropyl-2-(5-(4-methyl-2-(phenylphosphonyl)oxy)ethyl)-4-oxo-5-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)carbamate. Its molecular formula is C_{38}H_{31}FN_{10}O_{10}P and the structural formula is:

![Sofosbuvir structure]

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

- 90mg + 400mg (each film-coated tablet contain: Ledipasvir 90mg & Sofosbuvir 400mg)
- 400mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Ledipasvir and sofosbuvir are inhibitors of NS5A and NS5B, respectively, which are two essential enzymes required for HCV replication and the assembly of HCV virions. Resistance selection in cell culture and cross-resistance in vivo and in vitro have been observed when ledipasvir or sofosbuvir is administered alone or in combination.

Pharmacokinetics
Following oral administration of ledipasvir and sofosbuvir to HCV-infected patients, ledipasvir median systemic exposure (AUC_{0-24}) was 619 mcg·h/L (range, 580–739 mcg·h/L) and the lead peak plasma concentration was observed ~1.8 hours post dose. Median peak plasma concentration of GS-331007 was observed between 3.5 to 4 hours post dose. Ledipasvir AUC_{0-inf} is dose proportional over the dose range of 3 to 100mg. Sofosbuvir AUC_{0-inf} is also dose proportional over the dose range of 250mg to 1000mg.

Effect of Food
In a single dose, ledipasvir & sofosbuvir were observed to be absorbed from the GI tract and peak plasma concentrations were achieved 4-4.5 hours post dose. Fasting status did not affect the extent of absorption of ledipasvir or sofosbuvir.

Distribution
Ledipasvir is greater than 99.9% bound to human plasma proteins. After a single 90mg dose of (*)ledipasvir in healthy subjects, the blood plasma ratio of Ledipasvir concentration exceeds 90%.

Elimination
Ledipasvir is eliminated almost exclusively in the urine (70% of the dose). Following a single 40mg oral dose of (*)ledipasvir, mean total recovery of the dose was greater than 99%, consisting of approximately 60%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (73%) 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-life of ledipasvir 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.

Patients with Severe Hepatic Impairment
Ledipasvir plasma exposure (AUC_{0-24}) 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_{0-24} was 100% and 140% higher in moderate and severe renal impairment, while the GS-331007 AUC_{0-24} was 120% and 140% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 120% and 140% higher in moderate and severe hepatic impairment.

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

COSGAGE 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

<table>
<thead>
<tr>
<th>Patient Population*</th>
<th>Treatment &amp; Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with genotype 1, 4, or 6 (Chronic Hep C)</td>
<td>Syneget-LS (Ledipasvir + Sofosbuvir) for 24 weeks</td>
</tr>
<tr>
<td>Patients without ribavirin</td>
<td>Syneget-LS for 12 weeks</td>
</tr>
<tr>
<td>Patients with ribavirin</td>
<td>Syneget-LS + ribavirin for 24 weeks</td>
</tr>
<tr>
<td>Patients with compensated cirrhosis</td>
<td>Syneget-LS + ribavirin for 12 weeks</td>
</tr>
<tr>
<td>Patients with decompensated cirrhosis</td>
<td>Syneget-LS + ribavirin for 24 weeks</td>
</tr>
<tr>
<td>Patients with genotype 2/3 Chronic Hepatitis C</td>
<td>Syneget-LS + ribavirin for 12 weeks</td>
</tr>
<tr>
<td>Patients with decompensated cirrhosis, irrespective of transplant status</td>
<td>Syneget-LS + ribavirin for 12 weeks</td>
</tr>
<tr>
<td>Patients with ribavirin</td>
<td>Syneget-LS + ribavirin for 24 weeks</td>
</tr>
</tbody>
</table>

*Indicates 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 1000-1200mg daily in 2 divided doses.

In patients with decompensated cirrhosis, ribavirin should be administered at a starting dose of 800mg daily. By dose level, the starting dose is increased 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

Laboratory values
Reduction (Hb decrease) in 1000mg/day

<table>
<thead>
<tr>
<th>Hb change</th>
<th>−1g/dL</th>
<th>&lt;12g/dL</th>
</tr>
</thead>
</table>

Hemoglobin in patients with renal disease

<table>
<thead>
<tr>
<th>Hb change</th>
<th>&lt; 12g/dL</th>
</tr>
</thead>
</table>

Hemoglobin in patients with history of stable chronic disease

<table>
<thead>
<tr>
<th>Hb change</th>
<th>&lt; 12g/dL</th>
</tr>
</thead>
</table>

Dose reduction in patients with anemia

If a dose is missed and is within 18 hours then patients should be instructed not 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 skip the missed dose and then patients should take the next dose at the usual time. Patients should be instructed not to take a double dose.

In patients taking ribavirin, if a dose is missed and the dose is missed more than 18 hours after the normal time, patients should be instructed not to take a double dose.

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**Therapeutic range and which are metabolized by these isoenzymes should be used with caution:** CYP3A4, CYP2C and UGT1A1. Compounds that are substrates of these enzymes may have interactions with BCRP and may increase intestinal absorption of co-administered substrates for these transporters.

**Potential for ledipasvir + sofosbuvir to affect other medicinal products**

**DRUG INTERACTIONS**

It is not known whether ledipasvir or sofosbuvir and its metabolites are excreted in human milk. Nursing Mother. childrenbearing potential or their male partners must use an effective form of contraception during co-administration with ledipasvir + sofosbuvir.

**Effects on ability to drive and use machines**

If ledipasvir + sofosbuvir is administered alone or in combination with ribavirin, the warnings and precautions for ribavirin should be considered. Patients should be cautioned about the risk of their ability to drive a car and operate machinery.

**Pregnancy**

If ledipasvir + sofosbuvir is administered alone or in combination with ribavirin, the warnings and precautions for ribavirin should be considered. Patients should be cautioned about the risk of their ability to drive a car and operate machinery.

**Hepatic impairment**

2 Moderate or severe hepatic impairment.

**Pediatric Population**

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

**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 m2) or end stage renal disease (ESRD) requiring hemodialysis.

**CONTRAINDICATIONS**

Ledipasvir + sofosbuvir is contraindicated in: - Patients with known hypersensitivity to ledipasvir or sofosbuvir or to any of the excipients of the product. - Co-administration with nusinersen. - 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 with anticoagulants (e.g., warfarin, dabigatran etexilate, oxaparin) or other antiplatelet agents (e.g., aspirin). - Use of antituberculosis medications that increase ledipasvir and sofosbuvir plasma concentrations and could result in loss of efficacy.

**PRECAUTIONS**

- Serious systemic bacteraemias may occur in patients taking amoxicillin, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced heart disease. Co-administration of antibiotics with ledipasvir + sofosbuvir is not recommended. - Because of the potential for an increase in QTc interval, patients should be monitored for signs of weakness, dizziness or near fainting. - Increased risk of hypoglycaemia in patients taking insulin or sulfonylureas.

**Herbal Supplements**

- St. John’s wort (Hypericum perforatum)
- Melatonin
- L-arginine
- Tribulus terrestris
- Melatonin may increase the concentration of digoxin.

**HMG-CoA Reductase Inhibitors**

- Atorvastatin
- Simvastatin
- Pravastatin
- Lovastatin
- Fluvastatin
- Rosuvastatin
- Higher risk of rhabdomyolysis and myopathy. Clinical and biochemical control is recommended in these patients. - Statin therapy is generally recommended when coadministered with ledipasvir + sofosbuvir. - For patients taking statins, the clinical monitoring of digoxin and the concentration and eGFR should be undertaken. - The monitoring of digoxin may increase the concentration of digoxin. - Proton-pump inhibitor doses comparable to omeprazole 20mg or lower can be administered with ledipasvir + sofosbuvir at a dose that does not decrease concentration of ledipasvir.

**Anticoagulants**

- Dabigatran etexilate
- Dabigatran is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir + sofosbuvir. Co-administration is not recommended.

**Antifungal**

- Itraconazole
- Fluconazole
- Ketoconazole
- Fluconazole is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir + sofosbuvir. Co-administration is not recommended.

**Antiviral**

- Ribavirin
- Ribavirin is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of ledipasvir + sofosbuvir. Co-administration is not recommended.

**HIV Antiretrovirals**

- Indinavir
- Saquinavir
- Amprenavir
- Darunavir/ritonavir or cobicistat. Coadministration of ledipasvir + sofosbuvir with indinavir or saquinavir is not recommended. Effects of increases in tenofovir concentrations in the setting of ledipasvir + sofosbuvir and HIV protease inhibitorcontaining or cobicistat has not been established. Consider alternative HIV or antiretroviral therapy to avoid increases in tenofovir concentrations.

**Regimens containing Tenofovir disoproxil fumarate and a protease inhibitor**

- Tenofovir disoproxil fumarate and a HIV protease inhibitor/ritonavir or cobicistat
- Concentrations of ledipasvir and sofosbuvir are increased when saquinavir is coadministered with ledipasvir + sofosbuvir. Co-administration of ledipasvir + sofosbuvir with saquinavir or ritonavir is not recommended.

**HCV Products**

- Peginterferon alfa-2a (disopropyl fumarate and a HIV protease inhibitor/ritonavir or cobicistat)
- Concentrations of ledipasvir and sofosbuvir are increased when cobicistat is coadministered with ledipasvir + sofosbuvir. Co-administration of ledipasvir + sofosbuvir with cobicistat is not recommended.

**Regimens containing Tenofovir disoproxil fumarate and a HCV protease inhibitor/ritonavir**

- Tenofovir disoproxil fumarate and a HIV protease inhibitor/ritonavir or cobicistat
- Monitor for tenofovir-associated adverse reactions. In patients receiving ledipasvir + sofosbuvir concurrently with a regimen containing tenofovir disoproxil fumarate without a HIV protease inhibitorcontaining or cobicistat.