Selected Properties of Sofosbuvir

Other names	Sovaldi®, GS-331007, GS-461203 Combination formulation: • Harvoni®: ledipasvir/sofosbuvir
Manufacturer	Gilead Sciences
Pharmacology/ Mechanism of Action	Sofosbuvir is a direct acting antiviral agent against the hepatitis C virus. This agent is a specific inhibitor of the NS5B RNA-dependent RNA polymerase that is essential for viral replication.
Activity	Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate, GS-461203 that can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Premature termination of RNA synthesis causes viral replication to stop leading to a rapid decline of HCV viral load. Sofosbuvir has demonstrated inhibition of polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a in HCV replicon assays. The approved indication for sofosbuvir is for those with chronic hepatitis C (CHC) as a component of a combination antiviral treatment. Specifically those with HCV genotype 1, 2, 3 or 4 infections, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV co-infection.
Resistance – genotypic	The activity of sofosbuvir against HCV NS5B polymerase has been reduced in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a by the following amino acid substitution, S282T. Site directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the viral replication capacity by 89% and 99% compared to the corresponding wild type. Similarly in biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed a decreased susceptibility to GS-461203 compared with respective wild types. Reduced activity has also been associated with an M289L substitution in genotype 2a, 5 and 6 replicons. <u>In clinical trials specifically examining subjects with hepatocellular carcinoma awaiting liver transplantation:</u> • Substitutions in L159F emerged in multiple subjects with GT1a or GT2b HCV who experienced virologic failure (breakthrough and relapse). • Substitutions L159F and/or C316N at baseline were associated with sofosbuvir breakthrough and relapse following transplant in multiple subjects infected with GT1b HCV. • Substitutions in S282R and L320F were detected by next generation sequencing in a subject infected with GT1a HCV with a partial treatment response.
Resistance – phenotypic	In phase 3 clinical trials treatment emergent substitutions L159F and V321A were detected in post baseline samples from GT3a- infected subjects. There was no detectable shift in the phenotypic susceptibility of sofosbuvir in those with L159F or

<table>
<tr><td></td><td>V321A substitutions.</td></tr>
<tr><td>Cross-Resistance</td><td>• There are no known overlapping mutations between sofosbuvir associated resistance substitution S282T and NS5A inhibitors or ribavirin.
• Similarly ribavirin associated resistance substitutions T390I and F415Y were susceptible to sofosbuvir.
• Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors.
• Sofosbuvir is also active against HCV replicons with NS3/4A protease inhibitor, NS5B non-nucleoside inhibitor and NS5A inhibitor resistant variants.</td></tr>
<tr><td>Oral Bioavailability</td><td>The absolute bioavailability of sofosbuvir was not specifically evaluated, however at least 80% of the administered dose was absorbed into systemic circulation based upon urinary recovery.</td></tr>
<tr><td>Effect of Food</td><td>There was no significant effect of a standardized high fat meal on sofosbuvir or GS-331007 Cmax or $AUC_{0\text{-}inf}$. Relative to fasting conditions the administration of sofosbuvir with a standardized high fat meal slowed the rate of absorption (high-fat meal versus fasted; prolonged Tmax 1.5 versus 0.5 hours) but did not significantly affect the extent of absorption.

Sofosbuvir can be administered without regard to food.</td></tr>
<tr><td>Protein Binding</td><td>• Sofosbuvir is 61-65% bound to human plasma protein
• Protein binding is independent of drug concentration over the range of 1 mcg/mL to 20 mcg/mL
• Protein binding of GS-331007 was minimal in human plasma</td></tr>
<tr><td>Vd</td><td></td></tr>
<tr><td>Tmax</td><td>Following oral administration, sofosbuvir was absorbed with a peak plasma concentration observed at 0.5-2 hour post-dose, independent of dose. Peak plasma concentration of the active metabolite GS-331007 was observed between 2 to 4 hours post dose.</td></tr>
<tr><td>Serum T ½</td><td>Following a single 400 mg oral dose 80% was recovered in the urine. The majority of the sofosbuvir dose recovered in the urine was GS-331007 (78%) whereas 3.5% was recovered as sofosbuvir.

In clinical studies the mean terminal half lives of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.</td></tr>
<tr><td>Drug Concentrations</td><td>The table below displays population pharmacokinetic data for subjects with genotype 1 to 6 HCV infection who were co-administered ribavirin (with or without pegylated interferon), the geometric mean steady state:

<table>
<tr><td></td><td>Sofosbuvir</td><td>GS-331007</td></tr>
<tr><td>Genotype 1-6 HCV infection, $AUC_{0\text{-}24}$</td><td>860 ng.hr/mL</td><td>7200 mg.hr/mL</td></tr>
</table>

In subjects infected with HCV the sofosbuvir $AUC_{0\text{-}24}$ was 36% higher whereas the GS-331007 $AUC_{0\text{-}24}$ was 39% lower when compared with healthy subjects administered sofosbuvir alone.

The steady state $C_{max,}$ based on population pharmacokinetics for GS-331007 in patients with genotype 1 to 6 HCV infection was 582 ng/mL. Relative to healthy</td></tr>
</table>

<table>
<tr><td></td><td>volunteers the C_{max} was 49% lower than in HCV-infected patients.

Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200-1200 mg.</td></tr>
<tr><td>Minimum target trough concentrations (for wildtype virus)</td><td>In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a, 4a and chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a ranged from 0.014 to 0.11 μM.

The table below displays median EC_{50} value and range of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates:
<table><tr><th>Genotype</th><th>EC_{50} value (μM)</th><th>Range</th></tr><tr><td>1a</td><td>0.062</td><td>0.029-0.128</td></tr><tr><td>1b</td><td>0.102</td><td>0.045-0.170</td></tr><tr><td>2</td><td>0.029</td><td>0.014-0.081</td></tr><tr><td>3a</td><td>0.081</td><td>0.024-0.181</td></tr></table>
In infectious virus assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a were 0.03 and 0.02 μM respectively.
The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.
Evaluation of sofosbuvir with interferon alpha or ribavirin showed no antagonistic effect in reducing HCV RNA levels within replicon cells.
There is approximately 65% homology of the HCV NS5B polymerase across HCV genotypes and since GS-461203 binds to a highly conserved region of RdRp, sofosbuvir is a pangenotypic inhibitor of the HCV NS5B with a high barrier to resistance.</td></tr>
<tr><td>CSF (% of serum)</td><td></td></tr>
<tr><td>Metabolism</td><td>Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203.
The metabolic pathway for activation involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A or carboxylesterase 1 and phosphoramidate cleavage by histidine triad nucleotide binding protein 1 followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway.
Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro.
After a single 400 mg dose of 14C-sofosbuvir, sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug related material systemic exposure, respectively.</td></tr>
<tr><td>Excretion</td><td>Sofosbuvir is primarily eliminated through the urine.

Following a single 400 mg dose of 14C-sofosbuvir, 80%, 14% and 2.5% of the dose was recovered in the urine, feces and expired air, respectively. The majority of the sofosbuvir dose recovered in the urine was GS-331007 (78%).</td></tr>
<tr><td>Dosing – Adult</td><td>Sofosbuvir monotherapy is not recommended for the treatment of CHC and</td></tr>
</table>

should only be prescribed with ribavirin or in combination with both ribavirin and peginterferon alfa (refer to table below).

The recommended dose for sofosbuvir is one 400 mg tablet, taken orally, once daily with or without food. **Dose reduction of sofosbuvir is not recommended.**

The table below displays treatment regimen and duration based on viral genotype and patient population:

	Treatment	**Duration (Canadian Monograph)**	**Duration (American Monograph)**
Treatment naïve patients with genotype 1 or 4 CHC	Sofosbuvir + peginterferon alfa[a] + ribavirin[b]	12 weeks	12 weeks
Patients with genotype 2 CHC	Sofosbuvir + ribavirin[b]	12 weeks	12 weeks
Patients with genotype 3 CHC	Sofosbuvir + ribavirin[b]	16 weeks	24 weeks

a. See peginterferon alfa prescribing information for dosing recommendation for patients with genotype 1 or 4 CHC
b. Dose of ribavirin is weight based (<75 kg = 1000 mg and ≥75 kg = 1200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤50 mL/min) require dose reduction; refer to ribavirin prescribing information.

Sofosbuvir in combination wit ribavirin for 24 weeks may be considered as a therapeutic option for CHC patients with genotype 1 infection who are ineligible to receive an interferon based regimen.

Patients with Hepatocellular Caricinoma Awaiting Liver Transplantation:

- Sofosbuvir in combination with ribavirin is recommended for up to 24 weeks (48 weeks in the American monograph) or until the time of transplantation, whichever occurs first, to prevent post transplant HCV reinfection.

Patients Coinfected with Hepatitis B (HBV)/HCV:

- The safety and efficacy of sofosbuvir has not been established in patients coinfected with HBV.

Patients Coinfected with HCV/HIV-1:

Genotype 2 and 3: sofosbuvir and ribavirin for 12 weeks have been evaluated in an open label clinical trial. 75% of patients with genotype 2 and 63% of patients with genotype 3 achieved sustained virologic response 4 weeks post treatment. The safety profile was similar in coinfected patients to that of monoinfected patients.

Dose Modification:

- Genotype 1 and 4: if a patient experiences a serious reaction potentially related to peginterferon alfa and/or ribavirin, the peginteferon alfa and/or ribavirin dose should be reduced or discontinued. Refer to peginterferon alfa and ribavirin prescribing information for dose modification or discontinuation information.
- Genotype 2 and 3: if a patient experiences a serious reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, until the adverse reaction abates or decreases in severity. Please refer to the

<table>
<tr><td></td><td>ribavirin prescribing information for dose modification or discontinuation information.

<u>Discontinuation:</u>
• If pegylated interferon/ribavirin or ribavirin are used in combination with sofosbuvir and are permanently discontinued sofosbuvir should also be discontinued.</td></tr>
<tr><td>Dosing – Pediatric</td><td>Safety and effectiveness of sofosbuvir in children less than 18 years of age have not been established.</td></tr>
<tr><td>Dosing- Geriatrics</td><td>Clinical studies of sofosbuvir did not include enough patients greater than or equal to 65 years of age to determine if there is a difference in response compared with younger patients. Use caution when administering sofosbuvir in elderly patients as they are at a greater risk for adverse events such as anemia due to age related decline in hepatic and renal function.</td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>No dose adjustment of sofosbuvir is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of sofosbuvir has not been established in patients with decompensated cirrhosis.

<u>Rationale based on Clinical Studies:</u>
• Sofosbuvir was studied in patients with HCV infection and moderate and severe hepatic impairment (Child-Pugh Class B and C) by administering 400 mg of sofosbuvir for 7 days.
• Compared to subjects with normal hepatic function sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment. The GS-331007 AUC_{0-24} was 18% and 9% higher in patients with moderate and severe hepatic impairment, respectively.
• Population pharmacokinetics of HCV infected patients indicated that cirrhosis has no clinically relevant effect on the exposure of sofosbuvir and GS-331007.</td></tr>
<tr><td>Adjust in Renal Failure/ Dialysis</td><td>• No dose adjustment is required for patients with mild or moderate renal impairment [(mild (eGFR ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2)].
• No dose recommendations can be given for patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or with end stage renal disease requiring hemodialysis due to higher exposures (up to 20 fold) of the predominant sofosbuvir metabolite.
• Refer to ribavirin and peginteferon prescribing information for patients with CrCl <50 mL/min.

<u>Rationale based on Clinical Studies:</u>

The table below displays the relative increase in AUC_{0-inf} in HCV negative patients with mild (eGFR ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR <30 mL/min/1.73m^2) and end stage renal disease requiring hemodialysis compared with patients with normal renal function (eGFR >80 mL/min/1.73m^2) following a single dose of 400 mg of sofosbuvir:
<table>
<tr><th>Degree of renal impairment</th><th>AUC_{0-inf} of sofosbuvir relative to patients with normal renal function</th><th>AUC_{0-inf} of GS-331007 relative to patients with normal renal function</th></tr>
<tr><td>Mild</td><td>61%</td><td>55%</td></tr>
</table></td></tr>
</table>

	Moderate	107%	88%
	Severe	171%	451%
	End Stage (dosed 1 hour before hemodialysis)	28%	1280%
	End Stage (dosed 1 hour after hemodialysis)	60%	2070%

*4 hour hemodialysis session removed 18% of the administered dose

In 10 HCV-infected patients with eGFR <30 mL/min, 24 weeks of sofosbuvir 200 mg plus ribavirin was safe and well tolerated. Despite rapid on-treatment viral suppression, SVR rates were low; hence the next study cohort of HCV-infected subjects with severe renal impairment will receive sofosbuvir 400 mg plus ribavirin.[Gane et al. AASLD 2014].

Toxicity

Most common adverse events (>20%):

Ribavirin combination: fatigue

Ribavirin + peginterferon alfa combination: fatigue, anemia, neutropenia, insomnia, headache and nausea

Other adverse events reported:

- Puritis
- Asthenia
- Pyrexia
- Severe depression (in patients with a pre-existing history of psychiatric illness), including suicidal ideation and suicide
- Pancytopneia (specifically in patients receiving concurrent pegylated interferon)
- Specifically in patients with HCV/HIV coinfection decreased appetite and upper respiratory tract infection were observed in more than 5% of patients

Laboratory abnormalities:

- Increased bilirubin, greater than 2.5 X the upper limit of normal (ULN)
    - Bilirubin levels peaked within the first 1 to 2 weeks of therapy and decreased and returned to baseline by post treatment week 4
    - Increased bilirubin was not associated with transaminase elevations
- Creatinine kinase, asymptomatic elevation of greater than or equal to 10XULN was observed in 0-2% of patients in clinical trials
- Lipase, asymptomatic elevations of greater than or equal to 3XULN were observed in 1-2% of patients in clinical trials

Effect of sofosbuvir on QT interval:

A study conducted in healthy volunteers evaluated the effect of single dose sofosbuvir 400 mg and 1200 mg on the QTc interval compared with moxifloxacin 400 mg single dose. At 1200 mg (three times the maximum recommended dose)

<table>
<tr><td></td><td>sofosbuvir does not prolong the QTc interval to any clinically relevant extent.</td></tr>
<tr><td>Pregnancy & Lactation</td><td>Sofosbuvir is used in combination with ribavirin +/- peginterferon alfa. Ribavirin may cause birth defects and/or death of the exposed fetus and animal studies have shown interferons have abortifacient effects. Extreme care must be taken to avoid pregnancy in female patients or in female partners of male patients.

When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, women of childbearing potential and their male partners must use two forms of effective non-hormonal methods of contraception during treatment and for at least 6 months after treatment.

Patients should notify their health care provider immediately in the event of a pregnancy. There is a Ribavirin Pregnancy Registry established to monitor maternal and fetal outcomes of pregnant women exposed to ribavirin.

<u>Animal Studies:</u>

No effects on fetal development have been observed in rats and rabbits at the highest tested doses.

<u>Lactation:</u>

It is not known if sofosbuvir or its metabolites are present in human breast milk.

<u>Animal Studies:</u>
The predominant metabolite GS-331007 was the primary component observed in the milk of lactating rats, without an effect on nursing pups. A risk benefit analysis should be undertaken in lactating mothers on ribavirin therapy, consult prescribing information for ribavirin recommendations during lactation.</td></tr>
<tr><td>Drug Interactions</td><td>Sofosbuvir and GS-331007 are not inhibitors of any CYP450 isoenzymes or UGT1A1.

Sofosbuvir is a P-gp substrate and breast cancer resistance protein (BCRP) substrate whereas GS-331007 is not.

<u>Effect of sofosbuvir’s on other drugs’ pharmacokinetics</u>

Sofosbuvir and GS-331007 are not inhibitors of P-gp and/or BCRP and are not expected to increase exposure of drugs that are substrates of these transporters.

<u>Effect of other drugs on sofosbuvir pharmacokinetics</u>

• Drugs that are potent P-gp inducers such as rifampin or St. John’s wort may reduce sofosbuvir plasma concentration leading to a reduced therapeutic effect of sofosbuvir. Thus sofosbuvir should not be used with potent P-gp inducers.
• Co-administration of sofosbuvir with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration. Therefore sofosbuvir may be given with P-gp and BCRP inhibitors.
• The table below displays the potential effect of specific drug classes on the concentration of sofosbuvir and GS-331007.

<table>
<tr><th>Concomitant Drug Class: Drug Name</th><th>Effect on Concentration</th><th>Clinical Comment</th></tr>
<tr><td>Analeptics:
Modafinil</td><td>Decreased sofosbuvir
Decreased GS-331007</td><td>Coadministration of sofosbuvir with modafinil is expected to decrease</td></tr>
</table>
</td></tr>
</table>

			the concentration of sofosbuvir, leading to a reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
	Anticonvulsants: Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	Decreased sofosbuvir Decreased GS-331007	Coadministration of sofosbuvir and anticonvulsants is expected to decrease the concentration of sofosbuvir, leading to a decreased therapeutic effect. Coadministration is not recommended.
	Antimycobacterials: Rifabutin Rifampin Rifapentine	Decreased sofosbuvir Decreased GS-331007	Coadministration of sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir leading to a reduced therapeutic effect. Coadministration is not recommended. Sofosbuvir should not be used with rifampin, a potent P-gp inducer.
	Herbal Supplements: St. John's Wort	Decreased sofosbuvir Decreased GS-331007	Sofosbuvir should not be used with St. John's wort, a potent P-gp inducer.
	HIV Protease Inhibitors: Tipranavir/ritonavir	Decreased sofosbuvir Decreased GS-331007	Coadministration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

<u>Interaction with antiretrovirals</u>

No dose adjustments are required when sofosbuvir is used in combination with the following antiretrovirals based on results from clinical trials:

- Darunavir/ritonavir
- Efavirenz
- Emtricitabine
- Raltegravir
- Rilpivirine
- Tenofovir

Baseline Assessment	Prior to initiating therapy with sofosbuvir treatment combination, the complete blood count with white blood cell differential count, liver function tests, bilirubin,

	creatinine kinase and lipase level must be evaluated in all patients.
Routine Labs	HCV RNA levels should be monitored at Week 4, 12 and 24, or at the end of treatment.
Dosage Forms	400 mg tablets for oral administration. DIN: 02418355. Harvoni® (ledipasvir 90 mg/sofosbuvir 400 mg) tablets: DIN 02432226.
Information on Crushing/ Splitting Tablets	Sofosbuvir tablets can be disintegrated in water, juice, or milk with minor stirring and pressure with a spoon. However, the stability of sofosbuvir in these liquids is unknown at this time. Furthermore, there are no studies evaluating the pharmacokinetic parameters of the disintegrated or crushed sofosbuvir tablet versus the whole tablet. In addition, a disintegrated or crushed sofosbuvir tablet may have an unpleasant taste.(Personal communication, Gilead Sciences Canada, December 2013).
Storage	• Store at room temperature below 30 ^{o}C • Dispense in original container • Do not use if seal over bottle opening is broken or missing

References:

Gane EJ, Robson RA, Bonacini M, et al. Safety, antiviral efficacy and pharmacokinetics of sofosbuvir in patients with severe renal impairment [abstract 966]. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 7-11, 2014, Boston, MA.

Gilead Sciences, Inc.. SOVALDI Product Monograph. Foster City, CA. December 6, 2013.

Gilead Sciences Canada, Inc. SOVALDI Product Monograph. Mississauga, ON. December 12, 2013.