Selected Properties of Ledipasvir

Other names	Harvoni® (ledipasvir and sofosbuvir), GS-5885
Manufacturer	Glilead
Pharmacology / Mechanism of Action	Ledipasvir prevents replication of the hepatitis C virus (HCV) by targeting non-structural protein 5A (NS5A) protein. Although the precise mechanism is poorly understood, data suggest inhibition of NS5A leads to blockade of hyperphosphorylation, which plays an essential role in viral replication.
Activity	Ledipasvir is only approved for the treatment of chronic infection caused by genotype 1 HCV. The safety and efficacy of ledipasvir has not been fully established for genotypes 2, 4, 5 or 6. Ledipasvir/sofosbuvir has only been studied in a phase II open-label trial in treatment-naïve patients with genotype 3.
Resistance – Genotypic	In cell culture In cell cultures, NS5A amino acid substitutions Y93H (in genotypes 1a and 1b) and Q30E (genotypes1a) significantly reduced susceptibility to ledipasvir (greater than a 1000-fold change in the Median Effective Concentration, or EC50). In clinical studies In Phase III clinical trials, 37 subjects experienced virologic failures with ledipasvir/sofosbuvir. Emergent NS5A resistance-associated substitutions were seen in 76% (n=22/29) of subjects with genotype 1a virus, and in 88% (n=7/8) with genotype 1b virus. Among subjects with genotype 1a, the most common substitutions identified at failure were Q30R, Y93H or N, and L31M. Among those with genotype 1b (88%, n = 7/8), the most common substitution identified at failure was Y93H. Other detected substitutions included: K24R, M28T/V, Q30H/K/L (genotype 1a) and L31V/M/I (genotype 1b). Persistence of resistance mutations In patients who received 3 day monotherapy treatment with ledipasvir, HCV NS5A resistant polymorphisms (present at baseline or selected during treatment) persisted in 100% of genotype 1a and 50% of genotype 1b-infected patients at 48 weeks following treatment cessation, suggesting long-term persistence of resistance.[Lawitz et al. 2012; Wong et al. 2013].
Resistance – Phenotypic	Phenotypic analyses demonstrated that the identified NS5A substitutions conferred a 20- to > 243-fold reduction in susceptibility to ledipasvir; however, viruses with these resistance-associated variants remained susceptible to sofosbuvir.
Cross-Resistance	Cross-resistance is not expected between ledipasvir and other classes of direct-acting antivirals with different mechanisms of action. Ledipasvir was fully active against sofosbuvir resistance (including substitution S282T in NS5B) and vice versa. Ledipasvir was also fully active against resistance-associated variants commonly known to other classes of HCV inhibitors, such as NS5B non-nucleoside inhibitors, NS3 protease inhibitors, and ribavirin. However, efficacy of ledipasvir has not been demonstrated if previous treatment failure was associated with an NS5A inhibitor regimen. Ledipasvir-associated resistance mutations confer cross-resistance to other first generation HCV NS5A inhibitors.[Nakamoto et al. 2014]
Oral Bioavailability	Ledipasvir is well-absorbed.
Effect of Food	Food does not affect systemic exposures of ledipasvir. No impact of moderate-fat or high-fat meal vs fasting on ledipasvir pharmacokinetics.[German et al. 2014]
Protein Binding	Following administration of a single 90 mg dose, ledipasvir is greater than 99.8% bound to human plasma proteins, with a blood/plasma ratio of 0.51 to 0.66.
Vd	N/A; however, in animal studies, 14C-ledipasvir-derived radioactivity was widely distributed to tissues after a single oral dose.

Tmax	Following oral administration, the time to peak plasma concentration of ledipasvir is 4 to 4.5 hours.
Serum T½	The mean terminal half-life of ledipasvir is approximately 47 hours.
Drug Concentrations	Relative to healthy subjects, the mean steady-state AUC_{0-24} and C_{max} was 24% and 32% lower, respectively, in HCV-infected patients, • Mean steady-state AUC_{0-24} : 7290 ngxhr/mL and the • Mean steady-state C_{max}: 323 ng/mL Variables such as age, body weight, gender, race, cirrhosis, ribavirin usage, and disease status do not have a clinically relevant impact on ledipasvir exposures in HCV-infected subjects.[Kirby et al. 2014]
Minimum Target Trough Concentrations (for wild-type virus)	**Genotype** / **Effective Concentration (50% reduction, EC50) Values** **1a**: Median EC50 = 0.018 nM (range 0.009-0.085 nM) 0.031 nM (in HCV replicon assays) **1b**: Median EC50 = 0.006 nM (range 0.004-0.007 □M) 0.004 nM (in HCV replicon assays) **2a**: EC50 = 21 nM (against replicons with L31 in NS5A) EC50 = 249 nM (against replicons with M31 in NS5A) **2b**: EC50 = 16 nM EC50 = 530 nM (against replicons with M31 in NS5A) **3**: EC50 = 168 nM **4a**: EC50 = 0.39 nM **5a**: EC50 = 0.15 nM **6a**: EC 50 = 1.1 nM
CSF (% of serum)	N/A; however, low levels of C14-ledipasvir-derived radioactivity were observed in the CNS
Metabolism	Although the exact mechanism remains unknown, evidence suggests ledipasvir undergoes slow oxidative metabolism to form the metabolite M19. There does not appear to be any appreciable metabolism by CYP and UGT1A1 enzymes. Systemic exposure appears to be almost exclusively parent drug. Ledipasvir is also a substrate of the drug transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP). However, it is not a substrate for any known hepatic uptake transporter (including OCT1, OATPP1B1 or OATPP1B3). Not an inhibitor or inducer of P450 or UGT. Weak inhibitor of P-gp and BRCP (intestinal, not systemic). Likely a weak inhibitor of OATP1B1/1B3.[Mathias et al. 2013]
Excretion	Elimination occurs primarily via the biliary route, resulting in 86% recovery in the feces (with approximately 70% of the administered dose as the unchanged parent drug and 2.2% as M19). Only 1% of the dose is renally eliminated (in urine).[Kirby et al. 2013]
Dosing – Adult	Indication: **Genotype 1** chronic hepatitis C mono-infection in adults with compensated liver disease

	Dosage	**Duration**
Adults who are **treatment-naive**		
with or without cirrhosis	One tablet daily	12 weeks*
*Treatment-naive patients without cirrhosis who have HCV RNA <6 million units/mL may be considered for therapy of 8 weeks duration.		
Adults who are **treatment-experienced**[#]		
without cirrhosis	One tablet daily	12 weeks

	with cirrhosis | | 24 weeks Note: tablet contains fixed dose of ledipasvir and sofosbuvir, taken by mouth, with or without food #Treatment experienced patients are defined as those who have failed treatment with either: 1) a regimen of peginterferon alfa and ribavirin, or 2) a regimen of an HCV protease inhibitor and peginterferon alfa and ribavirin. **Canadian labeling:** • Missed dose: If missed dose is within 18 hours of regularly scheduled time, administer as soon as possible; if >18 hours from regularly scheduled time, resume at next regularly scheduled dose (do not double dose). If patient vomits <5 hours after administration dose should be repeated; if >5 hours, resume administer at next regularly scheduled dose.
Dosing – Pediatric	The safety and efficacy of ledipasvir has not established in pediatric patients.
Dosage Adjustment in Liver Dysfunction	The kinetics of single and multiple-dose ledipasvir were evaluated in HCV-uninfected subjects with moderate (Child Pugh class B) or severe hepatic (Child Pugh class C) impairment. No clinically relevant changes in ledipasvir AUC were observed in moderate or severe hepatic impairment compared to matched subjects with normal hepatic function. Ledipasvir Cmax ↓ 36% and t1/2 was modestly prolonged in subjects with severe hepatic impairment, possibly due to lower absorption/bioavailability and reduced clearance. There was no effect of severe hepatic impairment on ledipasvir plasma protein binding. Study drugs were well tolerated.[German et al. 2013] Child-Pugh class A, B, or C: no dosage adjustment is necessary. Decompensated cirrhosis: There are no dosage adjustments provided in manufacturer's labeling. Safety and efficacy have not been established in patients with decompensated liver disease.
Dosage Adjustment in Renal Failure / Dialysis	Similar pharmacokinetic parameters post-administration of a single 90 mg dose of ledipasvir were seen between subjects with severe renal impairment (eGFR < 30 ml/min) and those with normal renal function. No dosage adjustment is required for patients with mild, moderate or severe renal impairment. [Mogalian et al. AASLD 2014] End stage renal disease (ESRD), including intermittent hemodialysis (IHD): Specific guidelines for dosage adjustments in these patients are not available.
Toxicity	**Adverse Events** Common (incidence ≥10%): • Neurologic: headache (11-17%); other: fatigue (13-18%) **Lab Abnormalities** In adult clinical trials with Genotype 1 HCV with compensated liver disease: High lipase level in serum, (≥3 x ULN): incidence 1-3% Elevated serum bilirubin (≥1.5 x ULN): incidence 1-3% **Effects on EKG** Results of a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three-period crossover trial (n=59) indicated that ledipasvir (120 mg twice daily for 10 days) did not have a significant effect on QTc interval prolongation.
Pregnancy and Lactation	**Pregnancy** U.S. Food and Drug Administration's Pregnancy Category: B (all trimesters) Studies evaluating ledipasvir use during human pregnancy have not been

	conducted. It is unknown if ledipasvir crosses the placenta. In animal-reproduction studies, administration of ledipasvir did not produce observable effects on fetal development at the highest doses tested. Pharmacokinetic data suggest at the recommended clinical dose, AUC exposure to ledipasvir in animals was between 2- and 4-fold the human exposure. **Lactation** Based on currently available evidence, the potential for toxicity in a newborn/infant cannot be excluded. Lactation studies with ledipasvir have not been conducted. Data from animal studies, however, indicate that ledipasvir was detectable in the milk of lactating rats, albeit with no observable effect on the nursing pups. Per U.S. labeling recommendations, the decision to breastfeed during therapy should take into account the risk of infant drug exposure and the benefits of treatment to the mother. Per Canadian labeling, however, mothers should be instructed to discontinue breastfeeding prior to initiating therapy with ledipasvir.

Drug Interactions	In general, the drug-drug interaction potential with ledipasvir is primarily limited to the process of intestinal absorption. Clinically relevant inhibition by ledipasvir in systemic circulation is not expected owing to a high degree of protein binding.
	
	Based on drug-interaction studies, no clinically relevant interactions are expected with the following select agents:
	• ARVs: NRTIs (abacavir, lamivudine, emtricitabine, tenofovir/TDF*), NNRTIs (efavirenz, rilpivirine), boosted-PIs (atazanavir/ritonavir, darunavir/ritonavir), or raltegravir
	  ○ Per U.S. product monograph, patients receiving ledipasvir as part of Harvoni concomitantly with Stribild or tenofovir DF and a boosted-PI should be monitored for tenofovir-associated reactions
	• Immunosuppressants: cyclosporine, tacrolimus
	• Narcotics: methadone
	• Statins: pravastatin
	• Oral contraceptives
	
	Potential for ledipasvir to affect concentrations of other drugs:
	Ledipasvir inhibits:
	• P-gp and BCRP, which may increase intestinal absorption of coadministered substrates of these transporters
	  ○ Digoxin: therapeutic concentration monitoring of digoxin is recommended with co-administration of ledipasvir
	• OATPP1B1 or OATPP1B3, BSEP and UGT1A1, but only at concentrations exceeding those achieved in clinic
	
	Potential for other drugs to affect concentrations of ledipasvir:
	Potent P-gp inducers in the intestine (i.e., rifampin,)
	• May significantly reduce ledipasivr plasma concentrations
	• Concurrent administration is not recommended with the following agents:
	  ○ Anticonvulsants: carbamazepine, phenytoin, phenobarbital or oxcarbazepine
	  ○ Antimycobacterials: rifampin, rifabutin
	  ○ St. John's wort
	
	Acid reducing agents
	• May decrease ledipasvir solubility (secondary to increases in pH)
	• Antacids: separate administration of ledipasvir by 4 hours
	• H2-receptor antagonists:

	○ Administer with or 12 hours apart from ledipasvir; ○ Do NOT exceed doses equivalent to famotidine 40 mg twice daily • Proton pump inhibitors: ○ Do NOT administer before ledipasvir ○ Do NOT exceed doses equivalent to omeprazole 20 mg P-gp and BCRP inhibitors • No clinically significant interaction noted in clinical trials when ledipasvir/sofosbuvir was administered with darunavir/ritonavir (P-gp inhibitors) or cyclosporine (a P-gp and BCRP inhibitor) • May be coadministered with ledipasvir (per FDA-labeling)
Baseline Assessment	1. Determination of hepatitis C genotype (prior to initiation of therapy) 2. Serum HCV-RNA 3. Laboratory parameters: bilirubin, liver enzymes, and serum creatinine
Routine Labs	1. Serum HCV-RNA during treatment, at the end of treatment, during treatment follow-up, and as clinically indicated. 2. Bilirubin, liver enzymes, and serum creatinine periodically and as clinically indicated.
Dosage Forms	Ledipasvir is commercially available as Harvoni, a single tablet coformulation of ledipasvir 90mg and sofosbuvir 400 mg
Storage	Store below 30 degrees C (86 degrees F)

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