Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions
A Quick Guide for Clinicians – November 2019

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Mechanism of Action and Route of Metabolism for Ledipasvir/Sofosbuvir (Harvoni®)

Medication	HCV Mechanism of Action	Route of Metabolism and Drug Interaction Potential
Ledipasvir/Sofosbuvir (Harvoni®)	NS5a inhibitor and NS5b polymerase inhibitor	• Ledipasvir is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Unknown metabolism via slow oxidative metabolism has been observed. • Sofosbuvir is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The intracellular metabolism of sofosbuvir is mediated by hydrolase and nucleotide phosphorylation pathways.

Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions with HIV Medications

Concurrent Medication	Recommendation and Clinical Comments
HIV Protease Inhibitors	
Atazanavir (Reyataz®) + ritonavir (Norvir®) Atazanavir/cobicistat (Evotaz®) Darunavir (Prezista®) + ritonavir (Norvir®) Darunavir/cobicistat (Prezcobix®, also contained in Symtuza®) Lopinavir/ritonavir (Kaletra®) Fosamprenavir (Lexiva®) + ritonavir (Norvir ®) Saquinavir (Invirase®) + ritonavir (Norvir®)	• Safety of increased tenofovir plasma levels when given as tenofovir disoproxil fumarate and used with ritonavir or cobicistat boosted protease inhibitors has not been established. • Interaction NOT expected when using with tenofovir alafenamide.
Tipranavir (Aptivus®) + ritonavir (Norvir®)	• Co-administration of ledipasvir/sofosbuvir with tipranavir + ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced efficacy. Co-administration not recommended.

Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions with HIV Medications

Concurrent Medication	Recommendation and Clinical Comment
HIV Non Nucleoside Reverse Transcriptase Inhibitors	
Efavirenz (Sustiva®, also contained in Atripla®, Symfi®, Symfi Lo®)	• Concurrent use at standard doses appropriate. • If using tenofovir disoproxil fumarate in combination with sofosbuvir/ledipasvir, monitor for tenofovir-associated adverse reactions.
Etravirine (Intelence®) Nevirapine (Viramune®) Rilpivirine (Edurant®, also in Odefsey® which contains tenofovir alafenamide, Juluca®)	• Concurrent use at standard doses appropriate.
Rilpivirine (Edurant®, also in Complera® which contains tenofovir disoproxil fumarate) Doravirine (Pifeltro®, also contained in Delstrigo®)	• Concurrent use at standard doses appropriate. • If using tenofovir disoproxil fumarate in combination with sofosbuvir/ledipasvir, monitor for tenofovir-associated adverse reactions.
HIV Integrase Strand Transfer Inhibitors	
Bictegravir/tenofovir alafenamide/emtricitabine (Biktarvy®) Dolutegravir (Tivicay®, also contained in Dovato®, Triumeq®, Juluca®)	• Concurrent use at standard doses appropriate.
Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (Stribild®)	• Increased tenofovir levels expected. Safety of concurrent ledipasvir/sofosbuvir with elvitegravir, cobicistat, emtricitabine and tenofovir has not been established. Co-administration not recommended.
Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (Genvoya®) Raltegravir (Isentress® Isentress HD®)	• Concurrent use at standard doses appropriate.
HIV Entry Inhibitors	
Maraviroc (Selzentry®)	• Concurrent use at standard doses appropriate.
Ibalizumab (Trogarzo®)	• Concurrent use at standard doses appropriate.

HIV Nucleoside/Nucleotide Reverse Transcriptase Inhibitors	
Abacavir (Ziagen®) Emtricitabine (Emtriva®) Lamivudine (Epivir®) Tenofovir Disoproxil Fumarate (Viread®, also contained in Cimduo® and Temixys®) Tenofovir Alafenamide (Descovy®) Stavudine (Zerit®)	• Concurrent use at standard doses appropriate. • If using tenofovir disoproxil fumarate in combination with sofosbuvir/ledipasvir, monitor for tenofovir-associated adverse reactions.
Didanosine (Videx EC®) Zidovudine (Retrovir®)	• When using ribavirin with ledipasvir/sofosbuvir, the use of didanosine or zidovudine should be avoided due to overlapping toxicity.

Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions with Common Primary Care Medications

Medication and or Class	Recommendation and Clinical Comment
Antacids	• Separate aluminum and magnesium containing antacids and ledipasvir/sofosbuvir administration by 4 hours.
H2-receptor antagonists	• Administer simultaneously with or 12 hours apart from ledipasvir/sofosbuvir. Do not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors	• If co-administration required, doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.
Antiarrhythmic – Amiodarone	• Significant bradycardia expected with concurrent use, especially in patients on beta-blockers, underlying cardiac abnormalities, or advanced liver disease. Co-administration not recommended. If concurrent use required, cardiac monitoring is recommended, see package insert for additional information.
Antiarrhythmic – Digoxin	• Increase in digoxin levels possible. Monitor digoxin levels.
Anticoagulant – warfarin	• Frequent INR monitoring during co-administration and after stopping therapy recommended.
Anticonvulsants – carbamazepine, oxcarbazepine, phenobarbital, phenytoin	• Significant decrease in ledipasvir/sofosbuvir levels expected. Co-administration not recommended.
Antimycobacterials – rifampin, rifabutin, rifapentine	• Significant decrease in ledipasvir/sofosbuvir levels expected. Co-administration not recommended.

Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions with Common Primary Care Medication, continued

Herbal products – St. John's Wort	• **Significant decrease in ledipasvir/sofosbuvir levels expected due to intestinal P-glycoprotein (P-gp) induction associated with St. John's Wort. Co-administration not recommended.**
HMG-CoA Reductase Inhibitors – Atorvastatin	• **Co-administration may lead to increased risk of myopathy and rhabdomyolysis. Monitor closely.**
HMG-CoA Reductase Inhibitors – Rosuvastatin	• **Significant increase in rosuvastatin levels when used with ledipasvir/sofosbuvir leading to increased risk of myopathy, including rhabdomyolysis. Co-administration not recommended.**
HCV Medication – Simeprevir	• **Significant increases in ledipasvir and simeprevir levels expected. Co-administration not recommended.**

Disclaimer: The information contained in this table has been developed from various resources, including FDA product information, abstracts and posters presented at national and international meetings, and from Recommendations for the Testing, Managing and Treating of Hepatitis C from AASLD and IDSA located at www.hivguidelines.org. While the tables contained in this guide are complete based upon references reviewed, there may be other medications that may also be contraindicated or should be co-administered with caution. Please consult additional resources as needed.

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