DRUG INTERACTIONS WITH SOFOSBUVIR

	Sofosbuvir (Sovaldi®, SOF, GS-7977, formerly PSI-7977) Gilead
Pharmacology	NS5B uridine nucleotide inhibitor
Adult Dose	400 mg QD; supplied as 400 mg tablets
Kinetic Characteristics	Nucleotide analog prodrug. Sofosbuvir enters hepatocytes and is converted to the active triphosphate (GS-461203). Sofosbuvir is a substrate of P-gp and BCRP. • No inhibiting or inducing effects on P450, UGT1A1 and drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP) GS-331007 (primary systemic nucleoside metabolite, accounts for >90% of systemic drug exposure): • Not a P-gp substrate • No inhibiting or inducing effects on P450, UGT1A1 and drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP) • No effect on renal transporters OAT1, OAT3, OCT2 or MATE1 • Principally eliminated in urine Demographic variables such as age, gender, BMI, race, and cirrhosis do not influence sofosbuvir or GS-331007 exposures. Exposures of sofosbuvir and GS-331007 in patients with HCV were 36% higher and 39% lower, respectively, than in healthy subjects.[1]
Effect of hepatic impairment	The pharmacokinetics of sofosbuvir 400 mg QD for 7 days was assessed in 8 HCV-infected subjects with moderate hepatic impairment (Child-Pugh B cirrhosis). Sofosbuvir was well-tolerated and resulted in similar systemic exposure of the systemic metabolite as non-cirrhotic subjects. Significant declines in HCV RNA were observed in all subjects. Viral kinetics were less profound than those observed in less advanced patients, possibly secondary to absorption and hepatic blood flow (shunting). Additional studies of individuals with advanced cirrhosis will be conducted to determine optimal duration of therapy in these patients.[2]
Effect of renal impairment	The pharmacokinetics of single dose sofosbuvir 400 mg was assessed in subjects with varying degrees of renal impairment and end-stage renal disease (ESRD). Subjects with mild (eGFR 50-80 mL/min/1.73 m2), moderate (eGFR 30-49 mL/min/1.73 m2) and severe (eGFR < 30 mL/min/1.73 m2) renal impairment had approximately 56%, 90%, and 456% ↑ AUC of PSI-6206 (inactive nucleoside metabolite), respectively, than subjects with normal renal function.[3] Dose modification of sofosbuvir is not required in patients with HCV with Clcr ≥30 mL/minute.[1] 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.[4] In subjects with ESRD, hemodialysis extracted ~15% of sofosbuvir and 53% of PSI-6206 from plasma. Recommendations will also be made for sofosbuvir administration in patients undergoing hemodialysis.[3]

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Directly Acting Antivirals:	
Daclatasvir (NS5A inhibitor)	In an open-label randomized PK substudy in HCV-infected patients, subjects received sofosbuvir 400 mg QD for 7 days before initiation of daclatasvir 60 mg QD for a total of 24 weeks. Exposures of the sofosbuvir metabolite GW-331007 were similar in the presence and absence of daclatasvir, while sofosbuvir exposures were approximately 35% ↑ in the presence of daclastasvir. Daclatasvir exposures were similar to historical controls. These findings suggest the absence of a clinically relevant interaction between daclatasvir and sofosbuvir.[5]
Ledipasvir (NS5A inhibitor, GS-5885), GS-9669 (NS5B Thumb II polymerase inhibitor)	In an open-label, fixed-sequence, cross-over study in healthy volunteers, no clinically significant interactions were observed between sofosbuvir 400 mg and either ledipasvir 90 mg QD, GS-9669 500 mg QD, or the combination of ledipasvir with GS-9669. Sofosbuvir AUC was ↑ 2.3-fold by ledipasvir, ↑ 1.4-fold by GS-9669, and ↑ 3-fold by ledipasvir and GS-9669, which corresponded to increases in total drug-related material of 26%, 15% and 40%, respectively. These changes were not considered clinically significant, and the pharmacokinetics of the circulating metabolite GS-331007 were unaffected. Similarly, the pharmacokinetics of ledipasvir and GS-9669 were unaffected by coadministration of sofosbuvir. No dose adjustment of sofosbuvir, ledipasvir, or GS-9669 is required with coadministration.[6]
GS-5816 (second generation NS5A inhibitor)	In an open-label, fixed-sequence, cross-over, drug-drug interaction study, healthy subjects received either SOF 400 mg, GS-5816 150 mg daily, or both; all doses were administered with food. When SOF was coadministered with GS-5816, SOF plasma exposure ↑~1.8-2.4-fold, likely due to inhibition of intestinal P-gp and/or BCRP, and Cmax of GS-331007 (the predominant circulating nucleoside metabolite of SOF) ↓ ~35%. These changes are not considered clinically significant. The kinetics of GS-5816 were not altered in the presence of SOF. Sofosbuvir and GS-5816 may be coadministered without dose adjustment.[7]
Antiretrovirals:	
Darunavir/ritonavir	In an open-label, fixed-sequence, four-cohort study, healthy volunteers (n=19) received SOF 400 mg single dose (with food), underwent 3 day washout, then received darunavir 800/100 mg QD for 10 days, followed by the addition of single dose SOF 400 mg with darunavir 800/100 mg with food. DRV/r increased SOF AUC0-last 37%, AUC0-inf 34%, and Cmax 45%, likely by inhibition of P-gp. Darunavir AUC and Cmax ↓ 3% and Cmin ↓ 14% when coadministered with SOF. These changes are not considered clinically significant and dose adjustments are not warranted.[8]
Efavirenz	In an open-label, fixed-sequence, four-cohort study, healthy volunteers (n=17) received SOF 400 mg single dose (fasted), underwent 3 day washout, then received Atripla® (efavirenz 600 mg/ emtricitabine/ tenofovir) QD for 14 days, followed by the addition of single dose SOF 400 mg with Atripla®. In the presence of Atripla®, SOF ↓ AUC0-last 6.2%, ↓ AUC0-inf 5.9%, and Cmax ↓ 19%, while GS-331007 Cmax ↓ 23%. Efavirenz AUC ↓ 3.6%, Cmax ↓ 5.3% and Ctau ↓4.2% when coadministered with SOF. These changes are not considered clinically significant and dose adjustments are not warranted.[8]
Raltegravir	In an open-label, fixed-sequence, four-cohort study, healthy volunteers (n=19) received SOF 400 mg single dose (fasted), underwent 3 day washout, then received raltegravir 400 mg BID for 10 days, followed by the addition of single dose SOF 400 mg with raltegravir. In the presence of raltegravir, SOF ↓ AUC0-last 5.3%, ↓ AUC0-inf 5.4%, and Cmax ↓ 12.7%, while GS-331007 PK

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	parameters were unchanged. Raltegravir AUC ↓ 27% and Cmax ↓ 43% when coadministered with SOF. These changes comparable to historical data when raltegravir was coadministered with efavirenz or tipranavir/ ritonavir, dose adjustments are not warranted.[8]
Rilpivirine	In an open-label, fixed-sequence, four-cohort study, healthy volunteers (n=17) received SOF 400 mg single dose (with food), underwent 3 day washout, then received rilpivirine 25 QD for 10 days, followed by the addition of single dose SOF 400 mg with rilpivirine. In the presence of rilpivirine, SOF AUC ↑ 10% and Cmax ↑ 21%, while GS-331007 PK parameters were unchanged. Rilpivirine AUC ↑ 6%, Cmax ↑ 5% when coadministered with SOF. These changes are not considered clinically significant and dose adjustments are not warranted.[8]
Tenofovir	In an open-label, fixed-sequence, four-cohort study, healthy volunteers (n=17) received SOF 400 mg single dose (fasted), underwent 3 day washout, then received Atripla® (efavirenz 600 mg/ emtricitabine/ tenofovir) QD for 14 days, followed by the addition of single dose SOF 400 mg with Atripla®. In the presence of Atripla®, SOF ↓ AUC0-last 6.2%, ↓ AUC0-inf 5.9%, and Cmax ↓ 19%, while GS-331007 Cmax ↓ 23%. Tenofovir Cmax ↑ 25% when coadministered with SOF. These changes are not considered clinically significant and dose adjustments are not warranted.[8]
Other Drugs:	
Amiodarone	Serious risk of symptomatic bradycardia if amiodarone is co-administered with sofosbuvir/ledipasvir or sofosbuvir plus another DAA. In post-marketing reports, bradycardia was observed within hours to days of starting a SOF-DAA (ledipasvir, daclatasvir or simeprevir) regimen in patients also on amiodarone. Symptomatic bradycardia, one fatal cardiac arrest, and cases requiring pacemaker insertion have been observed. Risk factors include co-administration of a beta-blocker, underlying cardiac comorbidities, or advanced liver disease. The mechanism of this potential interaction is unknown. **Avoid coadministration of amiodarone with sofosbuvir-containing DAA regimens.** If amiodarone therapy is needed, in-patient cardiac monitoring for the first 48 hours of coadministration is recommended, followed by daily outpatient or self-monitoring of heart rate for at least the first 2 weeks of treatment.(Dear Health Care Provider letter, Gilead Sciences, March 2015)
Methadone	In 14 HCV-negative subjects on stable methadone (30-105 mg daily), administration of sofosbuvir 400 mg QD did not result in a significant effect on the pharmacokinetics of either R-methadone (1% ↑ Cmax and AUC) or S-methadone (5% ↓ Cmax and AUC) and no subjects experienced symptoms of opiate withdrawal. Sofosbuvir and methadone may be coadministered without dose adjustment.[9]
Oral contraceptives	In HCV-uninfected women on hormonal contraception with norgestimate/ethinyl estradiol (NGM/EE, Ortho Tri-Cyclen Lo®), administration of sofosbuvir for 7 days resulted in 19% ↑ AUC and 23% ↑ Ctau of NGM. Sofosbuvir kinetics were similar to historical data. FSH, LH and progesterone values were similar in all cycles. No loss in contraceptive efficacy is expected upon administration of combined oral contraceptives containing ethinyl estradiol and norgestimate with sofosbuvir or sofosbuvir/ledipasvir fixed dose combination.[10]
Transplant drugs: cyclosporine and tacrolimus	In healthy volunteers, coadministration of sofosbuvir 400 mg and cyclosporine 600 mg or tacrolimus 5 mg did not result in clinically significant interactions (in the presence of sofosbuvir, cyclosporine AUC ↓ 2%, Cmax ↑ 6% while tacrolimus AUC ↑ 9% and Cmax ↓ 27%). Sofosbuvir AUC was increased 4-fold

| | in the presence of cyclosporine, which corresponded to ~10% ↑ in total drug-related material, which was not considered to be clinically significant; the exposure of the major circulating metabolite, GS-331007, was not changed in the presence of cyclosporine. Cyclosporine or tacrolimus may be coadministered with sofosbuvir, with no dose adjustment of sofosbuvir required.[11] |

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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