DRUG INTERACTIONS WITH GRAZOPREVIR AND ELBASVIR

	Grazoprevir (MK-5172) (Merck)	Elbasvir (MK-8742) (Merck)
Pharmacology	NS3/4A protease inhibitor	NS5A inhibitor
Adult Dose	*Investigational*: 100 mg once daily	*Investigational:* 50 mg once daily
	Being developed as an oral, once-daily, fixed-dose combination product.	
Kinetic Characteristics	Substrate of CYP3A4, P-gp and OATP1B1.[1] Inhibitor of CYP2C8, 3A4 (weak), UGT1A1 (weak) and possibly BCRP.	Substrate of CYP3A4, P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro. No age effect observed in young (22-45 yrs) vs elderly (65-78 yrs) males; ~33% higher AUC in elderly female vs male subjects after adjusting for body weight.[2]
Effect of hepatic impairment	In adult cirrhotic patients with Child-Pugh A (n=8) who received MK-5172 200mg daily for 10 days, MK-5172 exposures were increased approximately 2 fold (AUC increased 62%, Cmax increased 28%, C24 increased 92%) compared to healthy matched control subjects. In adult cirrhotic patients with Child-Pugh B (n=8) who received MK-5172 100 mg daily for 10 days, MK-5172 exposures were increased approximately 5 fold (AUC increased 4.88-fold, Cmax increased 5.52-fold, C24 increased 3.90-fold) compared to healthy matched control subjects. MK-5172 was well-tolerated in subjects with mild and moderate hepatic impairment. Dosing recommendations for Child-Pugh B and C will be based on results of future studies.[3]	In adult cirrhotic patients with either Child-Pugh A (n=8) or Child-Pugh B (n=7), single 50 mg oral doses of MK-8742 resulted in ↓ 24% AUC, 42% ↓ Cmax and 27% ↓ C24h in mild hepatic impairment and ↓ 14% AUC, 31% ↓ Cmax and 17% ↓ C24h in moderate hepatic impairment compared to historical healthy controls. These results are not clinically meaningful and support the administration of MK-8742 to patients with mild and moderate hepatic dysfunction.[4]
DAA Interactions:		
Daclatasvir	In an open-label, fixed-sequence, multiple-dose study, healthy subjects received 60 mg daclatasvir once daily for 7 days followed by a 4 day washout, then 200 mg MK-5172 once daily for 7 days, followed by the combination of 200 mg MK-5172 and 60 mg daclatasvir daily for 8 days. The steady-state kinetics of both daclatasvir and MK-5172 were not significantly altered when coadministered. Dose adjustments	

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	are not required with this combination.[5]	
MK-5172		In an open-label, multiple-dose study, healthy adult subjects received MK-5172 200 mg daily for 7 days. Following a 7 day washout, subjects received MK-8742 20 mg daily for 7 days, then both drugs together for 8 days. Coadministration did not result in clinically significant changes in pharmacokinetic parameters of either drug. The combination of MK-5172 and MK-8742 may be coadministered without dose adjustment.[6]
MK-8742	In an open-label, multiple-dose study, healthy adult subjects received MK-5172 200 mg daily for 7 days. Following a 7 day washout, subjects received MK-8742 20 mg daily for 7 days, then both drugs together for 8 days. Coadministration did not result in clinically significant changes in pharmacokinetic parameters of either drug. The combination of MK-5172 and MK-8742 may be coadministered without dose adjustment.[6]	
Antiretroviral Interactions:		
Atazanavir/ritonavir	In an open-label, 3 period study, healthy subjects received MK-5172 200 mg once daily for 7 days. After a 7 day washout, subjects received atazanavir/ritonavir 300/100 mg daily for 14 days, followed by coadministration of MK-5172 200 mg daily plus ATV/r daily for 7 days. The exposures of MK-5172 were significantly increased by atazanavir/ritonavir (10.58-fold increase AUC, 6.24-fold increase Cmax and 11.6-fold increase in C24 of MK-5172) compared to MK-5172 administered alone. Atazanavir exposures were modestly increased with MK-5172 coadministration (atazanavir AUC increased 43%, Cmax increased 12%, C24 increased 23%). **Coadministration of MK-5172**	In an open-label, 3 period study, healthy subjects received MK-8742 50 mg once daily for 14 days. After a 7 day washout, subjects received atazanavir/ritonavir 300/100 mg daily for 14 days, followed by coadministration of MK-8742 50 mg daily plus ATV/r daily for 7 days. MK-8742 did not significantly impact ATV exposures (atazanavir AUC GMR of 1.07). MK-8742 exposure was significantly increased in the presence of ATV/r (MK-8742 AUC GMR 4.76 [4.07, 5.56]. This increase is postulated to be secondary to CYP3A4/Pgp inhibition by ATV/r and potential inhibition of OATP-mediated disposition of MK-8742.[8]

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	with boosted atazanavir is not recommended.[7]	
Darunavir/ritonavir	In an open-label, 3 period study, healthy subjects received MK-5172 200 mg once daily for 7 days. After a 7 day washout, subjects received darunavir/ritonavir 600/100 mg BID for 14 days, followed by coadministration of MK-5172 200 mg daily plus darunavir/r BID for 7 days. The exposures of MK-5172 were significantly increased by darunavir/ritonavir (7.5-fold increase AUC, 5.27-fold increase Cmax and 8-fold increase in C24 of MK-5172) compared to MK-5172 administered alone. Darunavir exposures were similar with MK-5172 coadministration compared to darunavir/ritonavir administered alone (darunavir AUC increased 11%, Cmax increased 10% and no change in C24). **Coadministration of MK-5172 with boosted darunavir is not recommended.**[7]	In an open-label, 3 period study, healthy subjects received MK-8742 50 mg once daily for 14 days. After a 7 day washout, subjects received darunavir/ritonavir 600/100 mg BID for 14 days, followed by coadministration of MK-8742 50 mg daily plus DRV/r BID for 7 days. MK-8742 did not significantly impact DRV exposures (darunavir AUC GMR of 0.95). MK-8742 exposure was significantly increased in the presence of DRV/r (MK-8742 AUC GMR 1.66 [1.35, 2.05]. This increase is postulated to be secondary to CYP3A4/Pgp inhibition by DRV/r and potential inhibition of OATP-mediated disposition of MK-8742.[8]
Dolutegravir	In an open-label, fixed sequence study, 12 healthy subjects received a single dose of dolutegravir 50 mg followed by a 3 day washout, then grazoprevir 200/elbasvir 50 mg once daily for 11 days with a single dose of dolutegravir 50 mg on day nine. Dolutegravir pharmacokinetics were not significantly impacted in the presence of grazoprevir/elbasvir, and elbasvir pharmacokinetics were unchanged with dolutegravir coadministration. Grazoprevir exposures were decreased in the presence of dolutegravir (grazoprevir AUC ↓ 19%, Cmax ↓ 36% and C24 ↓ 14%); however, these changes are within the therapeutic window for grazoprevir. Dose adjustments are not required.[9]	
Efavirenz	In an open-label, fixed sequence study, 12 healthy subjects received MK-5172 200 mg once daily for 7 days followed by a 7-day washout, EFV 600 mg once daily for 14 days, and then 200 mg MK-5172 and 600 mg EFV coadministered once daily for 7 days. In the presence of steady-state EFV, MK-5172 AUC was decreased 84%, likely due to CYP3A4 induction by EFV. Efavirenz exposures were not significantly impacted when	In an open-label, fixed sequence study, 10 healthy subjects received MK-8742 50 mg once daily for 7 days followed by a 7-day washout, EFV 600 mg once daily for 14 days, and then 50 mg MK-8742 and 600 mg EFV coadministered once daily for 7 days. In the presence of steady-state EFV, MK-8742 AUC was decreased 54%, likely due to CYP3A4 induction by EFV. Efavirenz exposures were not significantly impacted when coadministered with MK-8742

	Grazoprevir (MK-5172) (Merck)	Elbasvir (MK-8742) (Merck)
	coadministered with MK-5172. Coadministration of MK-5172 with efavirenz may lead to subtherapeutic MK-5172 exposures.[10]	(efavirenz AUC decreased 18%).[11]
Lopinavir/ritonavir	In an open-label, 3 period study, healthy subjects received MK-5172 200 mg once daily for 7 days. After a 7 day washout, subjects received lopinavir/ritonavir 400/100 mg daily for 14 days, followed by coadministration of MK-5172 200 mg daily plus lopinavir/r BID for 7 days. The exposures of MK-5172 were significantly increased by lopinavir/ritonavir (12.86-fold increase AUC, 7.31-fold increase Cmax and 21.7-fold increase in C24 of MK-5172) compared to MK-5172 administered alone. Lopinavir exposures were similar with MK-5172 coadministration compared to lopinavir/ritonavir administered alone (lopinavir AUC increased 3%, Cmax and C24 decreased 3%). **Coadministration of MK-5172 with boosted lopinavir is not recommended.**[7]	In an open-label, 3 period study, healthy subjects received MK-8742 50 mg once daily for 14 days. After a 7 day washout, subjects received lopinavir/ritonavir 400/100 mg BID for 14 days, followed by coadministration of MK-8742 50 mg daily plus LPV/r BID for 7 days. MK-8742 did not significantly impact LPV exposures (lopinavir AUC GMR of 1.02). MK-8742 exposure was significantly increased in the presence of LPV/r (MK-8742 AUC GMR 3.71 [3.05, 4.53]. This increase is postulated to be secondary to CYP3A4/Pgp inhibition by LPV/r and potential inhibition of OATP-mediated disposition of MK-8742.[8]
Raltegravir	In an open-label, multiple dose study, healthy subjects received raltegravir 400 mg BID for 4 days followed by an 8 day washout, MK-5172 200 mg daily for 7 days, then MK-5172 200 mg once daily and raltegravir 400 mg BID coadministered for 7 days. Raltegravir AUC was increased 43% and MK-5172 AUC decreased 9% during coadministration. These changes are not considered clinically meaningful and dose adjustments of raltegravir or MK-5172 are not required when given concomitantly.[12]	In an open-label, fixed sequence study, 10 subjects received a single dose of 400 mg RAL followed by a 4-day washout, a single dose of 50 mg MK-8742 followed by a 7-day washout, and then a single dose of 400 mg raltegravir coadministered with a single dose of 50 mg MK-8742. Exposures of both MK-8742 and RAL were not significantly altered when coadministered (RAL AUC GMR 1.02, MK-8742 GMR 0.81).[11]
Rilpivirine	In healthy subjects, coadministration of rilpivirine 25 mg daily plus grazoprevir 200 mg/elbasvir 50 mg daily for 9 days	In healthy subjects, coadministration of rilpivirine 25 mg daily plus grazoprevir 200 mg/elbasvir 50 mg daily for 9 days did not result in

	Grazoprevir (MK-5172) (Merck)	Elbasvir (MK-8742) (Merck)
	did not result in clinically meaningful impacts on exposures of grazoprevir, elbasvir, or rilpivirine. Combination may be coadministered without dose adjustment.[13]	clinically meaningful impacts on exposures of grazoprevir, elbasvir, or rilpivirine. Combination may be coadministered without dose adjustment.[13]
Ritonavir	In healthy subjects, coadministration of a single dose of MK-5172 200 mg and multiple dose ritonavir 100 mg BID led to a 2-fold increase in MK-5172 exposures. The combination was safe and well-tolerated.[1]	
Tenofovir	In an open-label, multiple dose study, healthy subjects received tenofovir 300 mg once daily for 7 days followed by an 8 day washout, MK-5172 200 mg daily for 7 days, then MK-5172 200 mg and tenofovir 300 mg coadministered once daily for 10 days. Tenofovir AUC was increased 18% and MK-5172 AUC decreased 14% during coadministration. These changes are not considered clinically meaningful and dose adjustments of tenofovir or MK-5172 are not required when given concomitantly.[12]	In an open-label, fixed sequence study, 10 healthy subjects received tenofovir 300 mg once daily for 7 days followed by a 7-day washout, 50 mg MK-8742 once daily for 8 days, then 50 mg MK-8742 and tenofovir 300 mg coadministered once daily for 7 days. Tenofovir AUC was increased 34% in the presence of MK-8742, while MK-8742 exposures were not significantly altered with coadministration (MK-8742 AUC decreased 7%). This interaction is not considered clinically meaningful.[11]
Other Drugs:		
Buprenorphine/naloxone	In 24 HCV-negative adults on stable opiate maintenance therapy with methadone (20-150 mg daily) or buprenorphine/naloxone (8/2-26/2 mg daily), coadministration of MK-5172 200 mg daily for 10 days did not significantly impact exposures of R-methadone (9% increase AUC), S-methadone (23% increase AUC), buprenorphine (2% decrease AUC) or naloxone (10% increase AUC). No symptoms of opiate toxicity or withdrawal were noted. The pharmacokinetics of MK-5172 in the presence of methadone or buprenorphine/naloxone were similar to historical data for MK-5172 administered alone. MK-5172 may be coadministered with methadone or buprenorphine/naloxone without dose adjustment.[14]	
HmgCoA reductase	In healthy subjects who received	In healthy subjects, administration of

	Grazoprevir (MK-5172) (Merck)	Elbasvir (MK-8742) (Merck)
inhibitors Atorvastatin Pitavastatin	single dose **atorvastatin 20 mg** alone or with multiple dose MK-5172 200 mg daily, atorvastatin AUC was increased 3-fold and Cmax increased 5.66-fold in the presence of MK-5172. This increase is likely due to CYP3A4 inhibition and possibly BCRP inhibition. The kinetics of MK-5172 were not significantly impacted by coadministration with atorvastatin.[15] In healthy subjects who received single dose **pitavastatin 1 mg** alone or with multiple dose MK-5172 200 mg daily, pitavastatin AUC was increased 11% in the presence of MK-5172, suggesting that MK-5172 is not an OATP inhibitor in vivo. The kinetics of MK-5172 were not significantly impacted by coadministration with pitavastatin.[15] In healthy subjects, administration of single dose **rosuvastatin 10 mg** with steady state grazoprevir 200 mg daily or the combination of grazoprevir 200 mg plus elbasvir 50 mg daily resulted in increased rosuvastatin exposures compared to rosuvastatin administered alone. Rosuvastatin AUC and Cmax were increased 59% and 325% respectively in the presence of grazoprevir, and increased 126% and 449%, respectively in the presence of grazoprevir plus elbasvir. These results suggest pre-systemic inhibition of rosuvastatin efflux by grazoprevir or grazoprevir/elbasvir in the liver and/or gut via BCRP inhibition. Rosuvastatin had no significant effects on grazoprevir or elbasvir exposures.[16] **May wish to avoid co-administration of rosuvastatin and grazoprevir/ elbasvir.** In healthy subjects, administration of single dose **pravastatin 40 mg** alone or with steady state grazoprevir 200 mg plus elbasvir 50	single dose rosuvastatin 10 mg with steady state grazoprevir 200 mg daily or the combination of grazoprevir 200 mg plus elbasvir 50 mg daily resulted in increased rosuvastatin exposures compared to rosuvastatin administered alone. Rosuvastatin AUC and Cmax were increased 59% and 325% respectively in the presence of grazoprevir, and increased 126% and 449%, respectively in the presence of grazoprevir plus elbasvir. These results suggest pre-systemic inhibition of rosuvastatin efflux by grazoprevir or grazoprevir/elbasvir in the liver and/or gut via BCRP inhibition. Rosuvastatin had no significant effects on grazoprevir or elbasvir exposures.[16] **May wish to avoid co-administration of rosuvastatin and grazoprevir/ elbasvir**. In healthy subjects, administration of single dose **pravastatin 40 mg** alone or with steady state grazoprevir 200 mg plus elbasvir 50 mg daily resulted in 33% increase AUC and 28% increase in Cmax of pravastatin, which was not considered clinically significant. Pravastatin had no significant effect on grazoprevir or elbasvir exposures.[16]

	Grazoprevir (MK-5172) (Merck)	Elbasvir (MK-8742) (Merck)
	mg daily resulted in 33% increase AUC and 28% increase in Cmax of pravastatin, which was not considered clinically significant. Pravastatin had no significant effect on grazoprevir or elbasvir exposures.[16]	
Ketoconazole	Coadministration of MK-5172 and ketoconazole (a potent CYP3A4 and P-gp inhibitor) increased MK-5172 AUC approximately 3-fold.[1]	In healthy male subjects, the effect of multi-dose ketoconazole 400 mg QD on the pharmacokinetics of 50 mg single dose MK-8742 was evaluated. MK-8742 AUC ↑ 31%, Cmax ↓ 22% and C24h ↑ 38% in the presence of ketoconazole.[17]
Methadone	In 24 HCV-negative adults on stable opiate maintenance therapy with methadone (20-150 mg daily) or buprenorphine/naloxone (8/2-26/2 mg daily), coadministration of MK-5172 200 mg daily for 10 days did not significantly impact exposures of R-methadone (9% increase AUC), S-methadone (23% increase AUC), buprenorphine (2% decrease AUC) or naloxone (10% increase AUC). No symptoms of opiate toxicity or withdrawal were noted. The pharmacokinetics of MK-5172 in the presence of methadone or buprenorphine/naloxone were similar to historical data for MK-5172 administered alone. MK-5172 may be coadministered with methadone or buprenorphine/naloxone without dose adjustment.[14]	In 10 adult subjects on stable methadone maintenance therapy, administration of MK-8742 50 mg once daily for 10 days did not affect AUC of R or S-methadone, and no symptoms of opiate toxicity or withdrawal were observed. Exposures of MK-8742 in the presence of methadone were increased compared to historical controls (MK-8742 AUC increased 71%, Cmax increased 92%), but these changes are not considered clinically meaningful. MK-8742 may be coadministered with methadone without dose adjustment.[18]
Midazolam	In healthy subjects who received single dose **midazolam 2 mg/mL** alone or with multiple dose MK-5172 200 mg daily, midazolam AUC was 34%, suggesting that MK-5172 is a weak CYP3A4 inhibitor.[15]	
Oral Contraceptives	In 20 HCV-uninfected women, administration of MK-5172 200 mg once daily for 10 days did not significantly affect the pharmacokinetics of single-dose Nordette-28 (0.03 mg/EE/0.15 mg LNG). Ethinyl estradiol AUC and Cmax were increased 10% and 5%, respectively and levonorgestrel AUC and Cmax were increased 23% and decreased 7%,	In 20 HCV-uninfected women, administration of MK-8742 50 mg once daily for 13 days did not significantly affect the pharmacokinetics of single-dose Nordette-28 (0.03 mg EE/0.15 mg LNG).[20]

	Grazoprevir (MK-5172) (Merck)	Elbasvir (MK-8742) (Merck)
	respectively in the presence of MK-5172. These changes are not considered clinically significant.[19]	
Rifampin	In an open-label, multiple-dose study in 12 healthy adults, subjects received a single intravenous dose of rifampin 600 mg with a single oral dose of 200 mg MK-5172, followed by a 7-day washout. Subjects then received MK-5172 200 mg daily for 8 days, followed by coadministration of MK-5172 200 mg daily with rifampin 600 mg orally once daily for 14 days. Coadministration of MK-5172 and a single dose of IV rifampin led to 12.6-fold increase in AUC of MK-5172, while coadministration with a single dose of oral rifampin led to an 8.35-fold increase in MK-5172 AUC, presumably via P-gp and OATP inhibition by rifampin. Steady-state AUC of MK-5172 was not affected by multiple oral doses of rifampin (AUC decreased 7%), but C24h of MK-5172 was reduced by 85%. This is likely due to the net effect of OATP inhibition and CYP3A4/Pgp induction by chronic rifampin administration.[21] **Suggest avoiding coadministration until further data available.**	

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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