DRUG INTERACTIONS WITH CURRENT/INVESTIGATIONAL HEPATITIS C PROTEASE INHIBITORS

	Paritaprevir (Holkira Pak®/Viekira Pak®, ABT-450) *AbbVie*	**Simeprevir (GALEXOS®, *OLYSIO™ (USA)* SMV, TMC435) Janssen**	**Danoprevir (DNV, RG7227) *Roche***	**Grazoprevir (MK-5172) *Merck***
Pharmacology	NS3/4A protease inhibitor	NS3/4A protease inhibitor	Macrocyclic protease inhibitor	NS3/4A protease inhibitor
Adult Dose	150 mg once daily with ritonavir 100 mg once daily Co-formulated as 12.5 mg ombitasvir/75 mg ABT-450/50 mg ritonavir tablet (daily dose is 2 tablets once daily).	150 mg once daily with food (supplied as 150 mg capsule)	*Investigational*: Boosted with ritonavir 100/100 mg BID	*Investigational:* 100 mg QD Coformulated with elbasvir (MK-8742) in a fixed dose tablet.
Impact of Food	In healthy subjects, paritaprevir Cmax, and AUC were 11 to 19% higher under non-fasting conditions compared to fasting.[1] Take with food.	Simeprevir AUC ↑ ~60% and Tmax increases 1-1.5 hours when taken with food, regardless of meal type (normal or high-fat meal). Simeprevir should be taken with food.[2]	In healthy subjects, food (low-fat and high-fat meals) appeared to slightly prolong absorption, but did not alter overall absorption of danoprevir/ritonavir.[3] Danoprevir/ritonavir may be given with or without food.	
Kinetic Characteristics	Paritaprevir: Substrate of 3A4, P-gp, OATP1B1. Inhibits CYP2C8, UGT1A1, OATP1B1 and OATP1B3. Ombitasvir: substrate of 3A4, P-gp. Inhibits CYP2C8, UGT1A1. Dasabuvir: substrate of CYP2C8>3A4, 2D6, P-gp. Inhibits UGT1A1, OATP1B1.	Substrate of CYP3A4. Mild inhibitor of intestinal (but not hepatic) CYP3A4, and 1A2.[4] Simeprevir has no clinically relevant effects on CYP2C9, 2C19 and 2D6.[5] Simeprevir inhibits OATP1B1/3 and P-gp transporters.[2]		Substrate of CYP3A4, P-gp and OATP1B1.[6] Inhibitor of CYP2C8, 3A4 (weak), UGT1A1 (weak) and possibly BCRP.
Effect of hepatic impairment	Monograph recommendations on use in hepatic impairment:[7] • Mild hepatic impairment (Child Pugh A): no dose adjustment required • Moderate hepatic impairment (Child Pugh B): not recommended	Simeprevir exposures were approximately 2-fold higher in volunteers with moderate hepatic impairment (Child Pugh B) compared to matched healthy controls. In subjects with severe hepatic impairment (Child Pugh C), simeprevir exposures were 2-fold		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

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	• Severe hepatic impairment (Child Pugh C): contraindicated The pharmacokinetics of single-dose paritaprevir 200 mg/ritonavir 100 mg/ ombitasvir 25 mg and dasabuvir 400 mg were assessed in in subjects with mild, moderate, or severe hepatic impairment and compared to healthy controls. In subjects (n=6) with **mild hepatic impairment (Child-Pugh A)**, AUC of paritaprevir was comparable (± 30%) to subjects with normal hepatic function • In subjects with **moderate hepatic impairment (Child-Pugh B)**, AUC of paritaprevir was 62% higher than subjects with normal hepatic function. • In subjects with **severe hepatic impairment (Child-Pugh C)**, AUC of paritaprevir was 920% higher compared to subjects with normal hepatic function.	higher compared to those with moderate hepatic impairment and 3-fold higher compared to HCV-infected patients with compensated liver disease. No dose adjustments are required in Child Pugh A or B hepatic impairment. Further study in severe (Child Pugh C) hepatic impairment is planned.[8]		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.[9]
Effect of renal impairment	The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir were evaluated in non-HCV infected subjects with varying degrees of	No clinically significant differences in pharmacokinetics were observed in non HCV-infected volunteers with mild, moderate, or severe renal impairment.		

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	renal impairment: • Mild renal impairment (Clcr 60-89 mL/min): paritaprevir, ritonavir and dasabuvir AUC values increased by 19%, 42% and 21%, respectively, while ombitasvir AUC values were unchanged relative to subjects with normal renal function. • Moderate renal impairment (CLcr: 30 to 59 mL/min): paritaprevir, ritonavir and dasabuvir AUC values increased by 33%, 80% and 37%, respectively, while ombitasvir AUC values were unchanged relative to subjects with normal renal function. • Severe renal impairment (CLcr: 15 to 29 mL/min): paritaprevir, ritonavir and dasabuvir AUC values increased by 45%, 114% and 50%, respectively, while ombitasvir AUC values were unchanged relative to subjects with normal renal function. Changes in exposure of ombitasvir, paritaprevir, ritonavir and dasabuvir in non-	Dose adjustment of simeprevir is not required in renal dysfunction.		

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	HCV infected subjects with mild-, moderate- and severe renal impairment are not expected to be clinically relevant. No data are available on the use of Viekira Pak in non-HCV infected subjects with End Stage Renal Disease (ESRD).[7]			
DAA Interactions:				
Daclatasvir		With coadministration of simeprevir 150 mg daily and daclatasvir 60 mg daily, daclatasvir AUC increased 96%, Cmax increased 50%, Cmin increased 168%, and simeprevir AUC increased 44%, Cmax increased 39% and Cmin increased 49% compared to either drug administered alone. No dose adjustment of daclatasvir or simeprevir are required with coadministration.[10]		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 are not required with this combination.[11]
Antiretroviral Interactions:				
Atazanavir	In 24 healthy subjects, the impact of atazanavir 300 mg once daily on the kinetics of AbbVie's 3D regimen (paritaprevir / ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) was investigated. In the presence of atazanavir, paritaprevir AUC increased 94%, Cmax increased 46%	It is not recommended to coadminister simeprevir with ritonavir, cobicistat, boosted or unboosted HIV protease inhibitors.[13]		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.

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	and C24 increased 226%, likely secondary to inhibition of OATP1B1/B3. Ombitasvir AUC was decreased 17%, Cmax decreased 23% and C24 decreased 11%, while dasabuvir AUC decreased 18%, Cmax decreased 17% and C24 decreased 21% in the presence of atazanavir. Exposures of paritaprevir greater than 2-fold were safe and well tolerated in phase 2 studies. No dose adjustments for paritaprevir/ritonavir, ombitasvir and dasabuvir are required when dosed with atazanavir.[12]			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 with boosted atazanavir is not recommended.**[14]
Darunavir/ ritonavir	In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen (paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and darunavir 800 mg once daily or 600 mg/100 mg BID (2nd darunavir dose administered with additional ritonavir). With coadministration, darunavir Cmax and AUC were not significantly affected, but darunavir Ctroughs were 43-48% lower. With darunavir 800 mg plus the 3D regimen, darunavir Cmax decreased 8%, AUC	In an open-label, randomized, 3-way crossover study, healthy subjects received simeprevir 150 mg once daily alone, darunavir/ritonavir 800/100 mg mg once daily alone, or darunavir/ritonavir with 50 mg simeprevir once daily, each for 7 days. Simeprevir AUC ↑ 2.6-fold, Cmax ↑ 1.79-fold and Cmin ↑ 4.58-fold when given as 50 mg in the presence of darunavir/ritonavir compared to when given as 150 mg daily alone. Darunavir AUC ↑ 18%, Cmin ↑ 31% and ritonavir AUC ↑		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

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	decreased 24% and Ctrough decreased 48%, paritaprevir Cmax increased 54%, AUC increased 29% and Ctrough increased 30%, dasabuvir Cmax increased 10%, AUC decreased 6% and Ctrough decreased 10%, ombitasvir Cmax and AUC decreased 14% and Ctrough decreased 13%.[15] With darunavir 600 mg BID, darunavir Cmax decreased 13%, AUC decreased 20% and Ctrough decreased 43%, paritaprevir Cmax decreased 30%, AUC decreased 41% and Ctrough decreased 17%, dasabuvir Cmax decreased 16%, AUC decreased 27%, Ctrough decreased 46%, ombitasvir Cmax decreased 24% and AUC and Ctrough decreased 27%.[15] No dose adjustments for paritaprevir/ritonavir, ombitasvir, dasabuvir and darunavir once or twice daily are required when coadministered.[15]	32%, Cmin ↑ 44% when coadministered with simeprevir. Coadministration of simeprevir and DRV/r is not recommended due to a significant increase in simeprevir exposure in the presence of DRV/r, even after dose adjustment of simeprevir from 150mg QD to 50mg QD. Similar effects are likely to be seen with other ritonavir-boosted PIs.[16] It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.[13]		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.**[14]
Dolutegravir	Significant interaction not anticipated.	Significant interaction not anticipated.		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

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				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.[17]
Efavirenz	In healthy subjects, potential interactions were evaluated between paritaprevir /ritonavir 150/100 mg QD and dasabuvir 400 mg BID and efavirenz 600/tenofovir 300/emtricitabine 200 mg (Atripla) once daily. This study was prematurely discontinued due to adverse events (primarily neurological, gastrointestinal, ALT/AST elevations) in several subjects. Coadministration of efavirenz and the 3D regimen is **contraindicated** due to increased frequency of adverse events.[18]	In an open-label, randomized, 3-way crossover study, healthy subjects received simeprevir 150 mg once daily alone, efavirenz 600 mg once daily alone, or the combination, each for 14 days. With coadministration, simeprevir AUC ↓ 71%, Cmin ↓ 91% and efavirenz AUC ↓ 10% and Cmin ↓ 13%. **Co-administration of simeprevir and efavirenz or nevirapine should be avoided**.[19]		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 coadministered with MK-5172. Coadministration of MK-5172 with

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				efavirenz may lead to subtherapeutic MK-5172 exposures.[20]
Elvitegravir/ cobicistat		Not recommended with cobicistat-boosted regimens.[13, 21]		
Etravirine		**Not recommended** with etravirine.[13]		
Fosamprenavir/ ritonavir		It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.		
Lopinavir/ ritonavir	In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen (paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and lopinavir/ritonavir 400/100 mg BID or 800/200 mg QD. With coadministration, lopinavir Ctrough was 218% higher when administered once daily in the evening. Lopinavir Cmax, AUC, and Ctrough were otherwise not significantly impacted in the presence of the 3D regimen. With lopinavir 800/ritonavir 200 mg plus the 3D regimen, lopinavir Ctrough was increased 218%, paritaprevir Ctrough increased 8.23-fold and AUC increased 87%, dasabuvir Cmax decreased 64%, AUC decreased 66%, Ctrough decreased 53%, and ombitasvir	It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.		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%).

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	Cmax decreased 87%, AUC decreased 3% and Ctrough increased 24%.[15] With lopinavir 400/ritonavir 100 mg BID plus the 3D regimen, lopinavir Cmax decreased 13%, AUC decreased 6%, Ctrough increased 15%, paritaprevir exposures increased 2-fold, dasabuvir Ctrough decreased 32% and AUC and Cmax were unchanged, and ombitasvir Cmax increased 14%, AUC increased 17% and Ctrough increased 17%.[15] Coadministration of paritaprevir/ritonavir, ombitasvir and dasabuvir with lopinavir/ritonavir once or twice daily is **not recommended** due to higher incidence of gastrointestinal adverse effects and higher paritaprevir exposures (lopinavir Ctrough increased 218% when dosed once daily with 3D regimen).[15]			**Coadministration of MK-5172 with boosted lopinavir is not recommended.**[14]
Raltegravir	In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen (paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and raltegravir 400 mg BID.	In an open-label, randomized, 3-way crossover study, healthy subjects received simeprevir 150 mg once daily alone, raltegravir 400 mg BID alone, or the combination, each for 7 days. With		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

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	With coadministration, raltegravir pharmacokinetics were 100-134% higher while pharmacokinetics of the 3D regimen were unchanged. No dose adjustment is recommended when raltegravir and the 3D regimen are coadministered.[18]	coadministration, simeprevir AUC ↓ 11%, Cmin ↓ 14% and raltegravir AUC ↑ 8% and Cmin ↑ 14%. These changes are not considered clinically significant and dose adjustments are not required when raltegravir is coadministered with simeprevir.[19]		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.[22]
Rilpivirine	In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen (paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and rilpivirine 25 mg daily. With coadministration, rilpivirine pharmacokinetics were 116-273% higher, paritaprevir exposures were minimally affected (+/- 32%) and ombitasvir and dasabuvir pharmacokinetics were unchanged. Coadministration of rilpivirine with the 3D regimen is **not recommended,** as increased rilpivirine exposures may be associated with increased risk of QTc prolongation.[18]	In an open-label, randomized, 3-way crossover study, healthy subjects received simeprevir 150 mg once daily alone, rilpivirine 25 mg once daily alone, or the combination, each for 11 days. With coadministration, simeprevir AUC ↑ 6%, Cmin ↓ 4% and rilpivirine AUC ↑ 12% and Cmin ↑ 25%. These changes are not considered clinically significant and dose adjustments are not required when rilpivirine is coadministered with simeprevir.[19]		
Ritonavir	In healthy volunteers, paritaprevir exposures were significantly increased with ritonavir coadministration (~48-fold increase AUC,	In an open-label, single-arm, two-period, sequential crossover study in healthy adults (n=12) who received simeprevir 200 mg QD	Analysis of plasma samples of subjects from the ATLAS or DAUPHINE trials receiving danoprevir 900 mg BID detected	In healthy subjects, coadministration of a single dose of MK-5172 200 mg and multiple dose ritonavir 100 mg BID led to a 2-

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	~28-fold increase Cmax), and mean terminal t1/2 for paritaprevir was increased from 3 hours to 5-8 hours. Mean ritonavir Cmax and AUC values appeared to increase with increase in paritaprevir exposure. Significant boosting effect allows for once daily dosing of paritaprevir at lower doses while potentially improving the resistance profile.[1] Paritaprevir is coformulated with ritonavir and ombitasvir as part of AbbVie's 3D regimen.	alone or with ritonavir 100 mg BID for 7 days, a 14.3-, 4.7- and 7.2-fold ↑ in simeprevir Cmin, Cmax and AUC24h, respectively when coadministered with ritonavir vs. when given alone.[5] It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.	up to 20 different danoprevir metabolites, but none were detected in plasma samples of patients receiving danoprevir 200/ritonavir 100 mg BID. Evidence suggests that ritonavir inhibits danoprevir metabolism and reduces the formation of reactive metabolites, and may reduce the risk of ALT elevations associated with reactive metabolite formation.[23]	fold increase in MK-5172 exposures. The combination was safe and well-tolerated.[6]
Tenofovir	The pharmacokinetics of AbbVie's 3D regimen (paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen with and without emtricitabine 200 mg and tenofovir 300 mg once daily was assessed in healthy volunteers. The DAAs showed a minimal impact on tenofovir pharmacokinetics (tenofovir AUC increased 13%, Cmax increased 7%, Ctrough increased 24%).[12]	In an open-label, randomized, 3-way crossover study, healthy subjects received simeprevir 150 mg once daily alone, tenofovir 300 mg once daily alone, or the combination, each for 7 days. With coadministration, simeprevir AUC ↓ 14%, Cmin ↓ 7% and tenofovir AUC ↑ 18% and Cmin ↑ 24%. These changes are not considered clinically significant and dose adjustments are not required when tenofovir is coadministered with simeprevir.[19]		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.[22]

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Other Drugs:				
Alprazolam	When alprazolam 0.5 mg once daily was coadministered with the 3D regimen in healthy volunteers, alprazolam Cmax increased 9% and AUC increased 167%. Pharmacokinetics of the 3D regimen were unchanged in the presence of alprazolam. Monitor for symptoms of increased alprazolam exposure and modify dose if required.[7, 24]			
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.		

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		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)		
Amlodipine	When amlodipine 5 mg once daily was coadministered with the 3D regimen in healthy volunteers, amlodipine Cmax increased 26% and AUC increased 34%. Paritaprevir Cmax decreased 23%, AUC decreased 22% and dasabuvir and ombitasvir pharmacokinetics were unchanged in the presence of amlodipine. The dose of amlodipine and other calcium channel blockers should be decreased by 50% when coadministering with the 3D regimen.[24]			
Buprenorphine/ naloxone	In 38 subjects on stable opioid replacement therapy (n=19 methadone, n=19 buprenorphine), administration of			In 24 HCV-negative adults on stable opiate maintenance therapy with methadone (20-150 mg daily) or buprenorphine/naloxon

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	paritaprevir/ritonavir/ombitasvir (150/100/25 mg QD) plus dasabuvir 250 mg BID and ribavirin for 12 weeks, no clinically evident treatment-emergent drug-drug interactions were noted, and treatment was well tolerated.[25] In the presence of the 3D regimen, buprenorphine Cmax was increased 118% and AUC was increased 107% and naloxone AUC was increased 18% and AUC was increased 28%. No dose adjustment of buprenorphine/naloxone is required.[24] Monitor patient for sedation and cognitive effects.[7]			e (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.[26]
Caffeine		In healthy subjects, administration of single dose **caffeine 150 mg** in the presence of steady-state simeprevir 150 mg once daily led to 26% ↑ AUC of caffeine. This effect is not considered clinically relevant.[21]		
Carbamazepine	When carbamazepine 200 mg once daily for 3 days then 200 mg twice daily was coadministered with the 3D regimen in healthy volunteers, carbamazepine Cmax and AUC increased			

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	10% and 17%, respectively, while paritaprevir Cmax decreased 66%, AUC decreased 70%, dasabuvir Cmax decreased 55%, AUC decreased 70%, and ombitasvir Cmax decreased 31% and AUC decreased 30%. **Carbamazepine is contraindicated**.[7, 24]			
Cyclosporine	The impact of cyclosporine on the pharmacokinetics of AbbVie's 3D regimen (paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. In the presence of cyclosporine, paritaprevir exposures were modestly increased (AUC increased 72%, Cmax increased 44%, C24 increased 85%) and dasabuvir exposures were modestly decreased (AUC decreased 30%, Cmax decreased 34%, C24 decreased 24%). No dose adjustment for the DAAs is recommended when dosed with cyclosporine.[12] When initiating therapy with Viekira Pak, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine			

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	blood concentrations to determine subsequent dose modifications. Upon completion of Viekira Pak therapy, the appropriate time to resume baseline doses of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.[7] A phase 1 study demonstrated a 3-fold increase in cyclosporine half-life and 7-fold increase in tacrolimus half-life when administered concomitantly with the AbbVie 3D regimen. Therefore, for the open-label phase II study (M12-999, CORAL-I) of the 3D regimen plus ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection on stable cyclosporine or tacrolimus therapy, cyclosporine was reduced to 20% of the usual daily dose given once daily, while tacrolimus was reduced to either 0.5 mg once weekly or 0.2 mg every 3 days. Cyclosporine concentrations were maintained within the desired range with the			

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	recommended dosing modification (n=5). The tacrolimus dose was 0.5-1 mg at 1-2 week intervals for most patients, and tacrolimus trough levels were comparable pre-treatment and on-treatment (n=29).[27]			
Dextromethorphan		In healthy subjects, administration of single dose **dextromethorphan 30 mg** in the presence of steady-state simeprevir 150 mg once daily led to 8% ↑ AUC of dextromethorphan. This effect is not considered clinically relevant.[21]		
Digoxin	The pharmacokinetics of the P-gp substrate digoxin 0.5 mg once daily alone or with AbbVie's 3D regimen (paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. Pharmacokinetics of the 3D regimen were unchanged in the presence of digoxin. The DAAs showed a minimal impact on the pharmacokinetics of digoxin (AUC increased 16%, Cmax increased 15%, Ctrough increased 1%).[12] A priori dose adjustments of digoxin are not required when coadministering with the Viekira Pak;	In healthy subjects, administration of single dose digoxin 25 mg in the presence of steady-state simeprevir 150 mg once daily led to 39% ↑ AUC of digoxin, likely due to inhibition of P-gp by simeprevir.[21]		

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	monitoring of digoxin concentrations is recommended.[7, 24]			
Duloxetine	When duloxetine 60 mg once daily was coadministered with the 3D regimen in healthy volunteers, duloxetine Cmax decreased 21% and AUC decreased 24%. Pharmacokinetics of the 3D regimen were unchanged in the presence of duloxetine. Dose adjustment of duloxetine or the 3D regimen are not required with coadministration.[7, 24]			
Ergot derivatives: ergotamine dihydroergotamine ergonovine methylergonovin	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Ergot derivatives are contraindicated**.[7, 24]			
Erythromycin		In healthy volunteers, coadministration of erythromycin 500 mg TID and simeprevir 150 mg daily for 7 days led to a 7.47-fold ↑ simeprevir AUC and 90% ↑ erythromycin AUC. Coadministration of simeprevir with moderate-strong 3A4 inhibitors is not recommended.[21]		
Escitalopram	When escitalopram 10 mg once daily coadministered with the 3D regimen in healthy volunteers, escitalopram Cmax	In healthy subjects, administration of escitalopram 10 mg daily with steady-state simeprevir 150 mg once daily led to 3% ↑		

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	was unchanged and AUC decreased 13%. The pharmacokinetics of the 3D regimen were not significantly changed in the presence of escitalopram. Dose adjustment of escitalopram or the 3D regimen are not required with coadministration.[7, 24]	Cmax and no change in AUC or Cmin of escitalopram, and 20%↓ Cmax, 25% ↓ AUC and 32%↓ Cmin of simeprevir. These changes are not considered clinically significant.[28]		
Fluticasone	Potential for increased fluticasone concentrations with inhaled or nasal fluticasone which may reduce serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long term use.[7]			
Furosemide	When furosemide 20 mg once daily was coadministered with the 3D regimen in healthy volunteers, furosemide Cmax increased 42% and AUC increased 8%. Pharmacokinetics of the 3D regimen were unchanged in the presence of furosemide.[24] Clinical monitoring of patients is recommended and therapy should be individualized based on the patient's response.[7]			
Gemfibrozil	The impact of gemfibrozil 600 mg BID on the pharmacokinetics of AbbVie's 3D regimen (paritaprevir/ritonavir/ombitasvir 150/100/25			

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	mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. In the presence of gemfibrozil, dasabuvir Cmax increased 2-fold and AUC increased 11.3-fold and paritaprevir Cmax increased 21% and AUC increased 38%. **Gemfibrozil is contraindicated**.[7, 24]			
HmgCoA reductase inhibitors (statins): atorvastatin lovastatin pravastatin rosuvastatin simvastatin	The pharmacokinetics of pravastatin 10 mg or rosuvastatin 5 mg daily alone or with AbbVie's 3D regimen (paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. With coadministration, pravastatin Cmax was increased 37%, AUC was increased 82% and the pharmacokinetics of the 3D regimen were unchanged. The pravastatin dose should be reduced by 50% (maximum dose of 40 mg daily) with the 3D regimen.[7, 12] When rosuvastatin was coadministered with the 3D regimen, rosuvastatin Cmax increased 7-fold and AUC increased 2.6-fold, while paritaprevir Cmax increased 59% and AUC increased 52% and dasabuvir	In healthy subjects, administration of single dose **rosuvastatin** 10 mg in the presence of steady-state simeprevir 150 mg once daily led to 2.8-fold ↑ AUC of rosuvastatin, likely due to inhibition of OATP1B1 by simeprevir. In healthy volunteers, administration of single dose **atorvastatin 40 mg or simvastatin 40 mg** in the presence of steady-state simeprevir 150 mg once daily led to 2.1-fold ↑ AUC atorvastatin and 1.5-fold ↑ AUC simvastatin, likely due to inhibition of CYP3A and OATP by simeprevir[21] Lovastatin, pitavastatin, pravastatin: potential for increased statin concentrations secondary to inhibition of CYP3A4 and/or OATP1B1 by		In healthy subjects who received 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.[29] 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

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	and ombitasvir pharmacokinetics were unchanged. A maximum dose of 10 mg rosuvastatin should be used with the 3D regimen.[7, 12] **Lovastatin and simvastatin are contraindicated with the 3D regimen**.[7, 24]	simeprevir. Use lowest statin dose and monitor for toxicity.[13]		pitavastatin.[29]
H2-antagonists (including cimetidine, famotidine, nizatidine, ranitidine, etc.) **equivalent doses:* *H2RAs (treatment):* *Famotidine 20 mg BID or 40 mg qhs* *Nizatidine 150 mg BID or 300 mg qhs* *Ranitidine 150 mg BID or 300 mg qhs* *H2RAs (maintenance qhs dosing):* *Famotidine 20 mg* *Nizatidine 150 mg* *Ranitidine 150 mg*			In a randomized, open-label study, healthy volunteers received a single dose of danoprevir/ritonavir administered alone or with a single dose of ranitidine 150 mg. When administered concomitantly with ranitidine, danoprevir AUC ↓ 18%, Cmax ↑ 4% and C12h ↓ 12%. Ritonavir PK was similar to previously published data. These changes are not considered clinically significant, and danoprevir/r can be dosed in combination with H2-antagonists.[3]	
Ketoconazole	The impact of ketoconazole 400 mg daily on the pharmacokinetics of AbbVie's 3D regimen (paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. In the presence of ketoconazole,	Coadministration of simeprevir with moderate-strong 3A4 inhibitors is not recommended.[21]		Coadministration of MK-5172 and ketoconazole (a potent CYP3A4 and P-gp inhibitor) increased MK-5172 AUC approximately 3-fold.[6]

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	paritaprevir exposures were increased (AUC increased 2-fold, Cmax increased 37%), ritonavir AUC increased 57% and Cmax increased 27%, and dasabuvir AUC increased 42%, Cmax increased 15%[12] Ketoconazole Cmax increased 16% and AUC increased 117% in the presence of 3D regimen. No dose adjustment for the DAAs is recommended when dosed with ketoconazole; a maximum dose of ketoconazole 200 mg should be used with the 3D regimen.[7, 24]			
Methadone	In 38 subjects on stable opioid replacement therapy (n=19 methadone, n=19 buprenorphine), administration of paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD plus dasabuvir 250 mg BID and ribavirin for 12 weeks, no clinically evident treatment-emergent drug-drug interactions were noted, and treatment was well tolerated.[25] No dose adjustment of methadone is required when coadministering with the 3D regimen.[7, 24]	In 12 healthy subjects on stable methadone therapy (30-150 mg daily), administration of steady-state simeprevir 150 mg once daily for 7 days did not impact the kinetics of R-methadone or S-methadone. No a priori methadone dose adjustment is required when initiating simeprevir therapy. Simeprevir exposure when combined with methadone was relatively low compared to historical controls, but this reduction is not considered clinically relevant. No dose adjustment of simeprevir is required with methadone.[30]	In healthy subjects on stable methadone therapy (20-120 mg daily), administration of danoprevir 100 mg/ritonavir 100 mg BID for 10 days did not significantly alter unbound R and S methadone concentrations, and no instances of methadone withdrawal were noted. Dosage adjustment of methadone is necessary with coadministration of danoprevir/ritonavir.[31]	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/naloxon

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				e were similar to historical data for MK-5172 administered alone. MK-5172 may be coadministered with methadone or buprenorphine/naloxone without dose adjustment.[26]
Midazolam	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Oral midazolam is contraindicated**.[7, 24]			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.[29]
Oral Contraceptives	When coadministered with the 3D regimen in healthy volunteers, norethindrone Cmax and AUC decreased 17% and 9%, respectively. Progestin-only contraceptives may be used with the Viekira Pak.[7] Ethinyl estradiol-containing oral contraceptives are **contraindicated** with the Viekira Pak® due to the potential to increase ALT.[24] Discontinue ethinyl estradiol-containing medications prior to starting Viekira Pak® (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of	In healthy female volunteers, no clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone were observed when coadministered with simeprevir 150 mg daily for 10 days. Systemic hormonal contraceptives may be used with simeprevir.[32]		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%, respectively in the presence of MK-5172. These changes are not considered clinically significant.[33]

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	treatment.			
Phenobarbital	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Phenobarbital is contraindicated**.[7, 24]			
Phenytoin	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Phenytoin is contraindicated**.[7, 24]			
Pimozide	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Pimozide is contraindicated**.[7, 24]			
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc. **equivalent doses:* *PPIs (daily standard dose):* *Esomeprazole 20 mg* *Lansoprazole 30 mg* *Omeprazole 20 mg* *Pantoprazole 40 mg* *Rabeprazole 20 mg*	When omeprazole 40 mg once daily was coadministered with the 3D regimen in healthy volunteers, omeprazole Cmax and AUC decreased 38% and paritaprevir Cmax increased 19%, AUC increased 18%, dasabuvir Cmax increased 13% and AUC increased 8%, and ombitasvir Cmax increased 2% and AUC increased 5%.[24] Monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.[7]	In healthy subjects, administration of single dose **omeprazole 40 mg** in the presence of steady-state simeprevir 150 mg once daily led to 21% ↑ AUC of omeprazole. This effect is not considered clinically relevant.[21]	In a randomized, open-label study, healthy volunteers received a single dose of danoprevir/ritonavir administered alone or with a multiple doses of omeprazole 40 mg. When administered concomitantly with omeprazole, danoprevir AUC ↓ 17%, Cmax ↓ 8% and C12h was unchanged. Ritonavir PK was similar to previously published data. These changes are not considered clinically significant, and danoprevir/r can be dosed in combination with proton-pump inhibitors.[3]	
Rifampin	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Rifampin is**	In healthy subjects, administration of rifampin 600 mg daily with steady-state simeprevir 200 mg		In an open-label, multiple-dose study in 12 healthy adults, subjects received a single intravenous

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	contraindicated.[7, 24]	once daily led to 8% ↓ Cmax and no change in AUC of rifampin, while simeprevir Cmax ↑ 31%, AUC ↓ 48% and Cmin ↓ 92%. Use of this combination should be avoided.[5] Coadministration of simeprevir with moderate-strong 3A4 inducers is not recommended.[21]		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.[34] Suggest avoiding coadministration until further data available.
Salmeterol	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Salmeterol is not**			

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	recommended.[24] The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.[7]			
Sildenafil	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Sildenafil is contraindicated with the 3D regimen when used for the treatment of pulmonary arterial hypertension**.[7, 24]			
St. John's wort	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **St. John's wort is contraindicated**.[7, 24]			
Tacrolimus	A phase 1 study demonstrated a 3-fold increase in cyclosporine half-life and 7-fold increase in tacrolimus half-life when administered concomitantly with the AbbVie 3D regimen. Therefore, for the open-label phase II study (M12-999, CORAL-I) of the 3D regimen plus ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection on stable cyclosporine or tacrolimus therapy, cyclosporine was reduced to 20% of the usual daily dose given once daily, while			

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	tacrolimus was reduced to either 0.5 mg once weekly or 0.2 mg every 3 days. Cyclosporine concentrations were maintained within the desired range with the recommended dosing modification (n=5). The tacrolimus dose was 0.5-1 mg at 1-2 week intervals for most patients, and tacrolimus trough levels were comparable pre-treatment and on-treatment (n=29).[27] When initiating therapy with Viekira Pak, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day Viekira Pak is initiated. Beginning the day after Viekira Pak is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of Viekira Pak therapy, the appropriate time to resume pre-Viekira Pak dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations.			

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	Frequent assessment of renal function and tacrolimus related side effects is recommended.[7]			
Triazolam	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Triazolam is contraindicated**.[7, 24]			
Voriconazole	Coadministration is not recommended due to potential for decreased voriconazole concentrations.[7]			
Warfarin	When warfarin 5 mg once daily was coadministered with the 3D regimen in healthy volunteers, R-warfamin Cmax increased 6%, AUC decreased 12% and S-warfarin Cmax decreased 4% and AUC decreased 12%. Pharmacokinetics of the 3D regimen were unchanged in the presence of warfarin. No dose adjustment of warfarin is required when coadministering with the 3D regimen; monitor INR when initiating and discontinuing 3D regimen and adjust warfarin dosing if required.[7, 24]	In healthy subjects, administration of single dose warfarin 10 mg in the presence of steady-state simeprevir 150 mg once daily led to 4% ↑ AUC of S-warfarin. This change is not considered clinically significant.[21]		
Zolpidem	When zolpidem 5 mg once daily was coadministered with the 3D regimen in healthy volunteers, zolpidem Cmax decreased 6% and AUC decreased 4%. Paritaprevir Cmax decreased 37% and			

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	AUC decreased 32%, ombitasvir and dasabuvir kinetics were unchanged in the presence of zolpidem. Dose adjustment of zolpidem or the 3D regimen are not required with coadministration.[7, 24]			

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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