DRUG INTERACTIONS WITH ABBVIE'S 3D REGIMEN
(PARITAPREVIR/RITONAVIR, OMBITASVIR AND DASABUVIR)

	Holkira Pak® (Canada)/Viekira Pak® (US):		
	Paritaprevir (ABT-450) plus Ritonavir	**Ombitasvir (ABT-267)**	**Dasabuvir (ABT-333)**
Pharmacology	NS3/4A protease inhibitor	NS5A inhibitor	NS5B palm polymerase inhibitor
Adult Dose	150 mg once daily with ritonavir 100 mg once daily Co-formulated as 12.5 mg ombitasvir/75 mg paritaprevir/50 mg ritonavir tablet (daily dose is 2 tablets once daily).	25 mg once daily Co-formulated as 12.5 mg ombitasvir/75 mg paritaprevir/50 mg ritonavir tablet (daily dose is 2 tablets once daily).	250 mg BID Dose is 1 tablet twice daily.
Impact of Food	In healthy subjects, food increased the AUC of paritaprevir and ritonavir by up to 211% and 49%, respectively, compared to fasting. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal). Take with food without regard to fat or calorie content.[1]	In healthy subjects, food increased the AUC of ombitasvir by up to 82% compared to fasting. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal). Take with food without regard to fat or calorie content.[1]	In healthy subjects, food increased the AUC of dasabuvir by up to 30% compared to fasting. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal). Take with food without regard to fat or calorie content.[1] .
Kinetic Characteristics	Substrate of 3A4, P-gp, OATP1B1, OAT1B3, BCRP. Inhibits UGT1A1, OATP1B1 and OATP1B3.[1] Ritonavir inhibits CYP3A4 and BCRP.	Substrate of 3A4, P-gp, BCRP. Inhibits UGT1A1.[1]	Substrate of CYP2C8>3A4, P-gp, BCRP. Inhibits UGT1A1, BCRP.[1]
Effect of hepatic impairment	Monograph recommendations on use in hepatic impairment:[1] • Mild hepatic impairment (Child Pugh A): no dose adjustment required • Moderate hepatic impairment (Child Pugh B): not recommended • Severe hepatic impairment (Child Pugh C):	Monograph recommendations on use in hepatic impairment:[1] • Mild hepatic impairment (Child Pugh A): no dose adjustment required • Moderate hepatic impairment (Child Pugh B): not recommended • Severe hepatic impairment (Child Pugh C): contraindicated	Monograph recommendations on use in hepatic impairment:[1] • Mild hepatic impairment (Child Pugh A): no dose adjustment required • Moderate hepatic impairment (Child Pugh B): not recommended • Severe hepatic impairment (Child Pugh C): contraindicated The pharmacokinetics of

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	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.	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 ombitasvir was comparable (8% lower) to subjects with normal hepatic function • In subjects (n=6) with **moderate hepatic impairment (Child-Pugh B)**, AUC of ombitasvir was 30% lower than subjects with normal hepatic function. • In subjects(n=5) with **severe hepatic impairment (Child-Pugh C)**, AUC of ombitasvir and was 55% lower compared to subjects with normal hepatic function.	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 dasabuvir was comparable (17% higher) to subjects with normal hepatic function • In subjects (n=6) with **moderate hepatic impairment (Child-Pugh B)**, AUC of dasabuvir was 16% lower than subjects with normal hepatic function. • In subjects(n=5) with **severe hepatic impairment (Child-Pugh C)**, AUC of ombitasvir and was 319%% higher compared to subjects with normal hepatic function.[2]
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 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	The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir were evaluated in non-HCV infected subjects with varying degrees of 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	The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir were evaluated in non-HCV infected subjects with varying degrees of 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

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	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-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).[1]	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-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).[1]	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-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).[1]
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% 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.		

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Darunavir	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 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%.[3] 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%.[3] No dose adjustments for paritaprevir/ritonavir, ombitasvir, dasabuvir and darunavir once or twice daily are required when coadministered.[3]		
Dolutegravir	In healthy subjects, coadministration of the 3D regimen with dolutegravir 50 mg daily for 10 days led to 22-38% increase in dolutegravir pharmacokinetic parameters, while DAA and ritonavir exposures were up to 18% lower, with the exception of paritaprevir and ritonavir Ctroughs (up to 34% decrease), compared to either 3D or dolutegravir administered alone. These changes are not considered clinically significant and dolutegravir may be administered with the 3D regimen without dose adjustment.[4]		
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.[5]		
Etravirine	Etravirine is contraindicated with the 3D regimen due to the potential for decreased exposures of ombitasvir, paritaprevir, ritonavir and dasabuvir.[1]		
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 Cmax decreased 87%, AUC decreased 3% and Ctrough increased 24%.[3] 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%.[3]		

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	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 ABT-450 exposures (lopinavir Ctrough increased 218% when dosed once daily with 3D regimen).[3]		
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. 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.[1, 5]		
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.[5]		
Ritonavir	In healthy volunteers, paritaprevir exposures were significantly increased with ritonavir coadministration (~48-fold increase AUC, ~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.[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%).[7]		
Other Drugs:			
Acetaminophen	When single-dose hydromorphone 5 mg/acetaminophen 300 mg was administered in the presence of steady-state 3D regimen, hydrocodone exposures increased 27-90% compared to single-dose hydromorphone/acetaminophen administered alone. Acetaminophen Cmax and AUC were not affected by 3D coadministration to a clinically significant extent (≤17% increase). A 50% dose reduction for hydrocodone is recommended when coadministered with the 3D regimen. Acetaminophen may be coadministered with the 3D regimen without dose adjustment.[8]		

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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.[1, 9]		
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.[9]		
Buprenorphine/ naloxone	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.[10] 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.[9] Monitor patient for sedation and cognitive effects.[1]		
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 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**.[1, 9]		
Carisoprodol	When single-dose carisoprodol 250 mg was administered in the presence of steady-state 3D regimen, carisoprodol exposures decreased 38-46%, but exposures of meprobamate (carisoprodol metabolite) were not affected to a clinically significantly extent compared to single-dose carisoprodol administered alone. An increase in carisoprodol dose may be required with the 3D regimen.[8] Titrate dose according to response/toxicity.		
Cyclobenzaprine	When single-dose cyclobenzaprine 5 mg was administered in the presence of steady-state 3D regimen, cyclobenzaprine exposures decreased 32-40%, but exposures of norcyclobenzaprine (cyclobenzaprine metabolite) were not affected to a clinically significantly extent compared to single-dose cyclobenzaprine administered alone. An increase in cyclobenzaprine dose may be required with the 3D regimen.[8] Titrate dose according to response/toxicity.		
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.[7] When initiating therapy with Viekira Pak, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine 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.[1] 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		

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	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 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).[11]		
Diazepam	When single-dose diazepam 2 mg was administered in the presence of steady-state 3D regimen, diazepam Cmax ↑ 18%, AUC ↓ 22% while nordiazepam Cmax ↑ 10%, AUC ↓ 40% compared to single-dose diazepam administered alone. An increase in diazepam dose may be required with the 3D regimen.[8] Titrate dose according to response/toxicity.		
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%).[9] A priori dose adjustments of digoxin are not required when coadministering with the Viekira Pak; monitoring of digoxin concentrations is recommended.[1, 9]		
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.[1, 9]		
Ergot derivatives: ergotamine dihydroergotamine ergonovine methylergonovin	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Ergot derivatives are contraindicated**.[1, 9]		
Escitalopram	When escitalopram 10 mg once daily coadministered with the 3D regimen in healthy volunteers, escitalopram Cmax 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.[1, 9]		
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.[1]		
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.[9] Clinical monitoring of patients is recommended and therapy should be individualized based on the patient's response.[1]		
Gemfibrozil	The impact of gemfibrozil 600 mg BID 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 gemfibrozil, dasabuvir Cmax increased 2-fold and AUC increased 11.3-fold and paritaprevir Cmax increased 21% and AUC increased 38%. **Gemfibrozil is contraindicated**.[1, 9]		
HmgCoA reductase inhibitors (statins):	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		

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atorvastatin lovastatin pravastatin rosuvastatin simvastatin	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.[1, 7] 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 and ombitasvir pharmacokinetics were unchanged. A maximum dose of 10 mg rosuvastatin should be used with the 3D regimen.[1, 7] **Lovastatin and simvastatin are contraindicated with the 3D regimen**.[1, 9]		
Hydrocodone	When single-dose hydrocodone 5 mg/acetaminophen 300 mg was administered in the presence of steady-state 3D regimen, hydrocodone exposures increased 27-90% compared to single-dose hydrocodone/acetaminophen administered alone. A 50% dose reduction for hydrocodone is recommended when coadministered with the 3D regimen.[8]		
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, 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%[7] 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.[1, 9]		
Metformin	When single-dose metformin 500 mg was administered in the presence of steady-state 3D regimen, metformin exposures were not significantly affected (~23% decrease) compared to single-dose metformin administered alone. Metformin may be administered with the 3D regimen without dose adjustment.[8]		
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.[10] No dose adjustment of methadone is required when coadministering with the 3D regimen.[1, 9]		
Midazolam	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Oral midazolam is contraindicated**.[1, 9]		
Omeprazole **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%.[9] 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.[1]		
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.[1] Ethinyl estradiol-containing oral contraceptives are **contraindicated** with the Viekira Pak® due to the potential to increase ALT.[9] Discontinue ethinyl estradiol-containing		

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	medications prior to starting Viekira Pak® (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment.		
Phenobarbital	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Phenobarbital is contraindicated**.[1, 9]		
Phenytoin	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Phenytoin is contraindicated**.[1, 9]		
Pimozide	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Pimozide is contraindicated**.[1, 9]		
Rifampin	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Rifampin is contraindicated**.[1, 9]		
Salmeterol	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Salmeterol is not recommended**.[9] The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.[1]		
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**.[1, 9]		
St. John's wort	Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **St. John's wort is contraindicated**.[1, 9]		
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 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).[11] 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. Frequent assessment of renal function and tacrolimus related side effects is recommended.[1]		
Triazolam	Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Triazolam is contraindicated**.[1, 9]		
Trimethoprim-sulfamethoxazole	When single-dose 3D regimen was administered in the presence of steady-state trimethoprim-sulfamethoxazole, trimethoprim-sulfamethoxazole exposures were not significantly affected (~17-22% increase) compared to trimethoprim-sulfamethoxazole administered alone. Trimethoprim-sulfamethoxazole may be administered with the 3D regimen without dose adjustment.[8]		
Voriconazole	Coadministration is not recommended due to potential for decreased voriconazole concentrations.[1]		
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		

	Holkira Pak® (Canada)/Viekira Pak® (US):		
	Paritaprevir (ABT-450) plus Ritonavir	**Ombitasvir (ABT-267)**	**Dasabuvir (ABT-333)**
	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.[1, 9]		
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 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.[1, 9]		

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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