DRUG INTERACTIONS WITH HEPATITIS C PROTEASE INHIBITORS

	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	**Simeprevir (GALEXOS®, *OLYSIO™ (USA)* SMV, TMC435) Janssen**	**Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/Janssen**
Pharmacology	NS3/4A protease inhibitor	NS3/4A protease inhibitor	NS3/4A protease inhibitor
Adult Dose	800 mg po q8h with food (supplied as 200 mg capsules)	150 mg once daily with food (supplied as 150 mg capsule)	1125 mg po BID with food (supplied as 375 mg tablets)
Impact of Food	Boceprevir AUC ↑ 60% when administered with a meal vs on an empty stomach. The bioavailability of boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Therefore, boceprevir may be taken without regard to either meal type or timing.[1]	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]	Compared to a regular breakfast, telaprevir AUC ↓ by 73%, 39% and 26% after administration under fasting conditions, low-calorie/low fat breakfast, and low-calorie/high protein breakfast, respectively. Telaprevir AUC ↑ 20% with a high-fat breakfast.[3] Telaprevir should be taken with food (not low-fat).[4]
Kinetic Characteristics	Boceprevir undergoes biotransformation by CYP3A4, CYP3A5 and aldoketoreductases.[5] Boceprevir appears to be a strong, reversible inhibitor of CYP3A4 and p-glycoprotein.[6] In a healthy volunteer study, boceprevir does not appear to exert significant P-gp inhibition at clinically relevant concentrations.[7] Boceprevir may induce CYP2C9/2C19 in vivo.[8]	Substrate of CYP3A4. Mild inhibitor of intestinal (but not hepatic) CYP3A4, and 1A2.[9] Simeprevir has no clinically relevant effects on CYP2C9, 2C19 and 2D6.[10] Simeprevir inhibits OATP1B1/3 and P-gp transporters.[2]	Substrate and strong inhibitor of CYP3A4 and p-glycoprotein.[4] Telaprevir inhibits renal drug transporters OCT2, MATE1, OATP1B1 and OATP1B3.[11]
Effect of hepatic impairment		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 higher compared to those with moderate hepatic impairment and 3-fold higher compared to HCV-infected patients with compensated liver disease.	HCV-negative volunteers with no, mild or moderate hepatic impairment received telaprevir 750 mg as a single dose, then 750 mg q8h for 5 days. All subjects with hepatic impairment were cirrhotics. Mild hepatic impairment did not have a clinically significant effect on telaprevir AUC and Cmax, while moderate hepatic impairment resulted in 49% ↓ Cmax and 46% ↓ AUC of telaprevir compared to

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		No dose adjustments are required in Child Pugh A or B hepatic impairment. Further study in severe (Child Pugh C) hepatic impairment is planned.[12]	controls. A positive correlation between albumin levels and telaprevir exposure was observed.[13] Telaprevir is not is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. No dose adjustment of telaprevir is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6).[4]
Other	In a population pharmacokinetic analysis, no significant covariate effects on boceprevir pharmacokinetic parameters were identified for age, body weight, BMI, Black race, Asian race, renal function and hepatic function. A modest effect of gender (23% ↑ AUC and 22% ↑ Cmax in females) and HCV status (15-20% ↓ Cmax) was observed, but not anticipated to be clinically meaningful.[14]	No clinically significant differences in pharmacokinetics were observed in non HCV-infected volunteers with mild, moderate, or severe renal impairment. Dose adjustment of simeprevir is not required in renal dysfunction.	No dose adjustment is recommended for telaprevir in HCV-infected patients with mild, moderate or severe renal impairment.[4]
1) ANTIRETROVIRALS			
Atazanavir/ ritonavir	In healthy volunteers, coadministration of boceprevir and atazanavir/ritonavir resulted in 49% ↓ Ctrough, 35% ↓ AUC and 25% ↓ Cmax of atazanavir and ↓ 34% ritonavir AUC; boceprevir exposures were not altered.[15] In a pharmacokinetic substudy of ACTG A5294, HIV/HCV coinfected subjects on boosted atazanavir (n=11) experienced 30% ↓ AUC and 43% ↓ Cmin of atazanavir during boceprevir therapy compared to	It is not recommended to coadminister simeprevir with ritonavir, cobicistat, boosted or unboosted HIV protease inhibitors.[19]	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days followed by a washout and ATV/r 300/100 mg once daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 20% and Cmin ↓ 15%, while atazanavir AUC ↑ 17% and Cmin ↑ 85%.[20] In a pharmacokinetic

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	baseline. Boceprevir pharmacokinetics in the presence of atazanavir/ritonavir were not significantly different from historical data. These effects are similar to those observed in healthy volunteers.[16] Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[1] The European Medicine Agency stated that coadministration of boceprevir with ritonavir-boosted atazanavir may be considered on a case-by-case basis if deemed necessary in patients with suppressed HIV viral loads and with an HIV strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted in such cases.[17] In an open-label, phase II trial of treatment-experienced HIV/HCV genotype 1 patients virologically suppressed on atazanavir/ritonavir-based cART (n=7), pharmacokinetic parameters were assessed at baseline and after 4 weeks of BOC 800 mg TID with ribavirin/pegylated interferon. Compared to baseline, mean atazanavir AUC ↓ 51%, Ctau ↓ 34% and Cmax ↓ 41% in the presence of BOC/ribavirin/peg-IFN; mean atazanavir Ctau was 507.7 ug/L compared to 763.8 ug/L at baseline.[18]		substudy of ANRSHC26, the pharmacokinetics of atazanavir/ritonavir with pegylated interferon/ribavirin or with pegylated interferon/ribavirin/telaprevir were assessed in 16 HIV-HCV coinfected subjects. Twelve subjects completed all samples for PK analysis. In the presence of telaprevir, atazanavir Cmin increased 79% despite a lower (35% decrease AUC) exposure to ritonavir. This was associated with a mild increase in bilirubin concentrations.[21] In HIV/HCV co-infected subjects participating in a phase 2 randomized study of telaprevir vs. placebo plus pegylated-interferon plus ribavirin, the kinetics of telaprevir were compared in patients on stable ATV/r therapy to patients not receiving concomitant antiretroviral therapy. In patients receiving concomitant ATV/r, telaprevir Cavg was 9% ↑ compared to patients not receiving concomitant antiretroviral therapy. Median atazanavir concentrations were 16% higher during telaprevir treatment vs. before HCV treatment. Dose adjustment is not required when atazanavir/ritonavir is administered with telaprevir.[22] In an open-label sequential study in HIV/HCV coinfected subjects on an atazanavir/ritonavir-based regimen plus triple therapy with telaprevir 1125 mg BID, pharmacokinetic profiles were acquired before and after

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			switching from boosted to **unboosted atazanavir 200 mg q12h**. After ritonavir was withdrawn, telaprevir AUC, Cmax and Cmin increased by 19%, 12% and 18%, respectively, while atazanavir AUC, Cmax and Cmin increased by 39%, 19% and 48%, respectively.[23]
Atazanavir/ ritonavir plus elvitegravir			In healthy subjects, coadministration of elvitegravir 85 mg/atazanavir 300 mg/ritonavir 100 mg daily plus telaprevir 750 mg TID for 10 days did not result in clinically relevant changes in the pharmacokinetics of elvitegravir, atazanavir or telaprevir pharmacokinetics. Combination may be coadministered without dose adjustment.[24]
Darunavir/ ritonavir	In healthy volunteers, coadministration of boceprevir and darunavir/ritonavir resulted in 59% ↓ Ctrough, 44% ↓ AUC and ↓ 36% Cmax of darunavir and 27% ↓ ritonavir AUC, while boceprevir exposure was ↓ by 32%.[15] In a pharmacokinetic substudy of ACTG A5294, HIV/HCV coinfected subjects on darunavir/ritonavir BID (n=5) experienced 42% ↓ AUC, 32% ↓ Cmax and 64% ↓ Cmin of darunavir during boceprevir therapy compared to baseline. Boceprevir Cmin was 93% higher with no differences in AUC or Cmax in the presence of darunavir/ritonavir compared to historical data. These effects are similar to those observed in healthy volunteers.[16]	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 ↑ 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	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and DRV/r 600/100 mg twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 35% and Cmin ↓ 32%, while darunavir AUC ↓ 40% and Cmin ↓ 42%.[20] Darunavir/ritonavir and telaprevir should not be co-administered.[4] In 14 HIV/HCV coinfected patients on stable cART including darunavir 800/ritonavir 100 mg daily, initiation of telaprevir 750 mg TID plus pegylated interferon

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	Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[1]	simeprevir from 150mg QD to 50mg QD. Similar effects are likely to be seen with other ritonavir-boosted PIs.[25] It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.[19]	and ribavirin led to a reduction in total and unbound darunavir plasma concentrations (total darunavir Cmin ↓ 39%, AUC ↓ 47%, while unbound darunavir Cmin ↓ 33% and AUC ↓ 46%) compared to darunavir concentrations prior to starting telaprevir. Mean total concentrations of telaprevir were reduced compared with historical data, but appeared similar to the lowest quartile observed in prior telaprevir studies.[26] Similarly, in two HIV/HCV coinfected individuals receiving darunavir 800/100 mg QD, complete steady-state PK study was performed before and 4 weeks after starting telaprevir 750 mg TID. In the presence of telaprevir, darunavir total AUC ↓ 68-75% and unbound AUC ↓ 53-66%, total Cmax ↓ 70% and unbound Cmax ↓ 46-54% compared to baseline. In one patient, darunavir total Ctrough ↓ 97% and unbound Ctrough ↓ 93%, while in the second patient, total Ctrough ↓ 58% but unbound Ctrough ↑ 207%. Both patients completed 12 weeks of triple therapy and their HIV remained virologically suppressed.[27]
Dolutegravir	In healthy subjects, coadministration of dolutegravir 50 mg QD with BOC 800 mg TID for 10 days had no effect on plasma dolutegravir AUC or Cmax, while Ctau ↑ 8% compared to dolutegravir 50 mg QD administered alone. Dolutegravir may be administered with boceprevir		In healthy subjects, coadministration of dolutegravir 50 mg QD with TVR 750 mg TID for 10 days resulted in 25% ↑ AUC, 19% ↑ Cmax and 37% ↑ Ctau of dolutegravir compared to dolutegravir 50 mg QD administered alone. Telaprevir exposures in the presence of dolutegravir were

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	without dose adjustment.[28, 29]		similar to historical controls. Dolutegravir may be administered with telaprevir without dose adjustment.[28, 29]
Efavirenz	In healthy subjects, there was a slight reduction in BOC $AUC_{(0\text{-}8h)}$ and C_{max} (19% and 8%, respectively), and a 44% decrease in BOC C_{min} when co-administered with efavirenz. BOC slightly increased EFV $AUC_{(0\text{-}24h)}$ and C_{max} (20% and 11%, respectively).[6] In a pharmacokinetic substudy of ACTG A5294, HIV/HCV coinfected subjects on efavirenz (n=19) did not experience significant alterations in efavirenz pharmacokinetics during boceprevir therapy compared to baseline. Boceprevir Cmin ↓ 21%, AUC ↓ 11% and Cmax ↓ 27% in the presence of efavirenz compared to historical data. These effects are similar to those observed in healthy volunteers.[16] **Avoid combination**.[1]	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**.[30]	In healthy volunteers, multiple-dose administration of efavirenz 600 mg daily and telaprevir 750 mg q8h resulted in 9% ↓ Cmax, 47% ↓ Cmin and 26% ↓ AUC of telaprevir.[31] In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%, and tenofovir AUC ↑ 10% and Cmin ↑ 17%. With TVR 1500 mg q12h plus EFV/TDF, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%.[20] In HIV/HCV co-infected subjects participating in a phase 2 randomized study of telaprevir vs. placebo plus pegylated-interferon plus ribavirin, the kinetics of

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			telaprevir 1125 mg q8h were compared in patients on stable efavirenz therapy to patients on telaprevir 750 mg q8h not receiving concomitant antiretroviral therapy. In patients receiving efavirenz, telaprevir Cavg was 4% ↓ compared to patients not receiving concomitant antiretroviral therapy. Median efavirenz concentrations were 6% lower during telaprevir treatment vs. before HCV treatment. A higher dose of telaprevir (1125 mg every 8 hours) given with efavirenz provides similar telaprevir exposures as seen in the absence of efavirenz.[22]
Elvitegravir/ cobicistat	Potential for concentrations of DAA and/or elvitegravir/cobicistat to be affected; avoid coadministration until more data are available.	Not recommended with cobicistat-boosted regimens.[19, 32]	In healthy volunteers, coadministration of telaprevir 750 mg TID with elvitegravir/ cobicistat/tenofovir/emtricitabine (Stribild®) for 10 days did not result in clinically relevant changes in pharmacokinetic exposures of Stribild® or telaprevir. The combination may be coadministered without dosage adjustment.[33]
Etravirine	In healthy volunteers, coadministration of boceprevir 800 mg q8h with etravirine 200 mg BID for 11-14 days resulted in ↓ 23% AUC, ↓ 24% Cmax and ↓29% Cmin of etravirine and ↑10% AUC and Cmax and ↓ 12% Cmin of boceprevir compared to either drug administered alone. Impact on boceprevir concentrations not considered clinically relevant; impact on etravirine concentrations could be clinically significant.[34] Mechanism of interaction postulated to be induction of CYP2C9/19 by etravirine.[8]	**Not recommended** with etravirine.[19]	In healthy volunteers, coadministration of telaprevir 750 mg TID with etravirine 200 mg BID for 11 days resulted in ↓ 6% AUC, ↓ 7% Cmax and ↓3% Cmin of etravirine and ↓ 16% AUC, ↓ 10% Cmax and ↓ 25% Cmin of telaprevir compared to either drug administered alone. These changes are not considered clinically relevant, combination may be given without dose adjustment.[35]

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	The combination of etravirine and boceprevir can be used without dose adjustments. However, co-administration of etravirine and boceprevir is not recommended in the presence of other drugs which may further decrease etravirine exposure. This includes, but is not limited to, darunavir/ritonavir, lopinavir/ritonavir, saquinavir/ritonavir, tenofovir disoproxil fumarate, or rifabutin.[Intelence® revised Product Label, August 2014, Janssen, USA]		
Fosamprenavir/ ritonavir	Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[1]	It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and fosamprenavir/r 700/100 mg twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 32% and Cmin ↓ 30%, while amprenavir AUC ↓ 47% and Cmin ↓ 56%.[20] Fosamprenavir/ritonavir and telaprevir should not be co-administered.[4]
Lopinavir/ritonavir	In healthy volunteers, coadministration of boceprevir and lopinavir/ritonavir resulted in 43% ↓ Ctrough, 34% ↓ AUC and ↓ 30% Cmax of lopinavir and 22% ↓ ritonavir AUC, while boceprevir exposure was ↓ by 45%.[15] Coadministration of boceprevir and ritonavir-	It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and lopinavir/r 400/100 mg twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds

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	boosted protease inhibitors is not recommended.[1]		were taken with food. With coadministration, telaprevir AUC ↓ 54% and Cmin ↓ 52%, while lopinavir AUC ↑ 6% and Cmin ↑ 14%.[20] Lopinavir/ritonavir and telaprevir should not be co-administered.[4]
Maraviroc	In an open-label, fixed sequence study, 13 healthy volunteers received maraviroc 150 mg BID for 5 days, followed by BOC 800 mg TID plus maraviroc 150 mg BID for 10 days, then after a 10-day washout period, TVR 750 mg TID plus maraviroc 150 mg BID for 10 days. In the presence of BOC, maraviroc GMR for AUC was 3.02, Cmax 3.33, and C12 2.78 versus maraviroc administered alone. Boceprevir pharmacokinetics were similar to historical controls. The mean maraviroc Cavg was 151 ng/mL in combination with boceprevir.[36] In an open-label, crossover, single sequence study, healthy volunteers (n=5) received maraviroc 150 mg BID for 5 days followed by BOC 800 mg TID plus maraviroc 150 mg BID for 14 days. In the presence of BOC, maraviroc GMR for AUC was 2.28, Cmax 1.25, and Ctau 3.62 versus maraviroc administered alone. The mean maraviroc Ctau was 30 ng/mL (CV 69%) with BOC, versus 7 ng/mL (CV 52%) alone.[37] Maraviroc should be dosed at 150 mg BID when coadministered with		In an open-label, fixed sequence study, 13 healthy volunteers received maraviroc 150 mg BID for 5 days, followed by BOC 800 mg TID plus maraviroc 150 mg BID for 10 days, then after a 10-day washout period, TVR 750 mg TID plus maraviroc 150 mg BID for 10 days. In the presence of TVR, maraviroc GMR for AUC was 9.49, Cmax 7.81, and C12 10.17 versus maraviroc administered alone. Telaprevir pharmacokinetics were similar to historical controls. The mean maraviroc Cavg was 465 ng/mL in combination with telaprevir. Maraviroc should be dosed at 150 mg BID when coadministered with telaprevir.[36]

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	boceprevir.[36, 37]		
Raltegravir	In an open-label, randomized, cross-over study, 24 healthy volunteers, received boceprevir 800 mg TID for 10 days plus single dose raltegravir 400 mg on day 10 followed by a wash-out period and single-dose raltegravir 400 mg on day 38, or the same medications in reverse order. Raltegravir exposures were not altered in the presence of boceprevir. The combination may be used without dosage adjustment.[38] In a pharmacokinetic substudy of ACTG A5294, HIV/HCV coinfected subjects on raltegravir BID (n=17) experienced 56% ↑ AUC, 87% ↑ Cmax of raltegravir during boceprevir therapy compared to baseline. Boceprevir AUC was 18%% higher with no differences in Cmin or Cmax in the presence of raltegravir compared to historical data.[16] The safe use of raltegravir-based therapy in HIV-patients with HCV-cirrhosis receiving triple therapy with boceprevir (n=2) or telaprevir (n=9) has been reported. Median baseline CD4 was 556 cells/mm3, all subjects had undetectable viral load, and all subjects had compensated cirrhosis (Child-Pugh score ≤6 in 82%). During 12 weeks of triple therapy, HIV viral suppression was maintained in all patients except one due to nonadherence. 73% patients achieved complete	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 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.[30]	In an open-label cross-over study in 20 HIV/HCV-negative healthy volunteers, co-administration of raltegravir 400 mg BID and telaprevir 750 mg q8h for 6 days with food did not affect telaprevir pharmacokinetics, while raltegravir exposures were increased (Cmin ↑ 78%, Cmax ↑ 26% and AUC ↑ 31%) possibly due to inhibition of intestinal P-gp by telaprevir. Exposure to raltegravir-glucuronide was similarly increased. This effect was not considered to be clinically relevant.[40] No dose adjustment is needed for telaprevir when given with raltegravir. The safe use of raltegravir-based therapy in HIV-patients with HCV-cirrhosis receiving triple therapy with boceprevir (n=2) or telaprevir (n=9) has been reported. Median baseline CD4 was 556 cells/mm3, all subjects had undetectable viral load, and all subjects had compensated cirrhosis (Child-Pugh score ≤6 in 82%). During 12 weeks of triple therapy, HIV viral suppression was maintained in all patients except one due to nonadherence. 73% patients achieved complete early HCV virologic response (negative HCV-RNA at week 12 of therapy) with no breakthrough or recurrence during follow-up.[39]

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	early HCV virologic response (negative HCV-RNA at week 12 of therapy) with no breakthrough or recurrence during follow-up.[39] In an open-label, phase II trial of treatment-experienced HIV/HCV genotype 1 patients virologically suppressed on raltegravir-based cART (n=5), pharmacokinetic parameters were assessed at baseline and after 4 weeks of BOC 800 mg TID with ribavirin/pegylated interferon. Compared to baseline, mean raltegravir AUC ↑ 57%, Ctau ↓ 55% and Cmax ↑ 156% in the presence of BOC/ribavirin/peg-IFN.[18]		
Rilpivirine	In healthy volunteers (n=20), coadministration of boceprevir 800 mg TID and rilpivirine 25 mg QD for 11 days resulted in 39% ↑ AUC, 15% ↑ Cmax and 51% ↑ C24h of rilpivirine. The combination was well-tolerated, and these changes were not considered clinically significant. Boceprevir kinetics were not affected by coadministration of rilpivirine. Boceprevir and rilpivirine may be coadministered without dose adjustment.[41]	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.[30]	In healthy volunteers, coadministration of telaprevir 750 mg TID with rilpivirine 25 mg daily for 11 days resulted in ↑ 78% AUC, ↑ 49% Cmax and ↑ 93% Cmin of rilpivirine and ↓ 8% AUC, ↓ 5% Cmax and ↓ 13% Cmin of telaprevir compared to either drug administered alone. These changes are not considered clinically relevant, combination may be given without dose adjustment.[35] May wish to avoid using combination in patients at increased risk for Torsade de Pointes, or who are on other drugs that may ↑ rilpivirine levels or that are known to cause QTc prolongation.
Ritonavir	In human liver microsomes, the metabolism of telaprevir and boceprevir was substantially inhibited in the presence of low concentrations of ritonavir.	In an open-label, single-arm, two-period, sequential crossover study in healthy adults (n=12) who received simeprevir 200 mg QD alone or with ritonavir 100 mg BID	In human liver microsomes, the metabolism of telaprevir and boceprevir was substantially inhibited in the presence of low concentrations of ritonavir.

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	With co-dosing of ritonavir in rats, the plasma exposure of both HCV agents was increased by more than 15-fold, and plasma concentrations 8 hours after dosing were increased by > 50-fold.[42] In healthy subjects, ritonavir had minimal effects on steady-state BOC exposure. RTV 100 mg daily plus BOC three times daily resulted in BOC AUC ↓ 19% and Cmax ↓ 27%, while ritonavir 100mg BID plus BOC twice daily resulted in decreased BOC AUC by 18% and Cmax ↓ 34%.[6]	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.[10] It is not recommended to coadminister simeprevir with ritonavir, boosted or unboosted HIV protease inhibitors.	With co-dosing of ritonavir in rats, the plasma exposure of both HCV agents was increased by more than 15-fold, and plasma concentrations 8 hours after dosing were increased by > 50-fold. A human pharmacokinetic model of telaprevir co-administered with low-dose ritonavir suggested that improved efficacy and/or dosing convenience may be feasible by pharmacokinetic enhancement with ritonavir.[42] HIV-negative subjects received telaprevir 750 mg q8h alone, or 250 mg or 750 mg BID with ritonavir 100 mg BID. Doses were given with food for 14 days. Ritonavir did not exert a significant boosting effect on telaprevir exposures: when compared with TVR 750 mg q8h given alone (Group C), TVR PK parameters on Day 14 were 59% to 75% lower when TVR 250 mg q12h was co-administered with RTV 100 mg q12h (Group A) and 15% to 32% lower when TVR 750 mg q12h was co-administered with RTV 100 mg q12h (Group B). Of note, RTV exposures were higher when co-administered with TVR 750 mg q12h (Group B), compared with 250 q12h (Group A), suggesting that CYP3A inhibition by TVR was dose-dependent.[43]
Tenofovir	In healthy subjects, there were no clinically relevant changes in BOC exposure when co-administered with tenofovir. BOC also had no notable effect on tenofovir AUC or renal clearance, but increased tenofovir C_{max} by	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,	In a randomized, open-label study, healthy volunteers received tenofovir 300 mg daily, telaprevir 750 mg q8h, or both drugs, each for 7 days. In the presence of telaprevir, tenofovir AUC_{24h} was increased by 30% while

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	32%. No BOC dosage adjustment is needed with co-administration tenofovir.[6]	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.[30]	telaprevir kinetics were not affected.[44] In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF/FTC, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%, and tenofovir AUC ↑ 10% and Cmin ↑ 17%. With TVR 1500 mg q8h plus EFV/TDF/FTC, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%.[20]
2) OTHER MEDICATIONS			
Amlodipine	Combination not studied. Potential for ↑ amlodipine concentrations in the presence of boceprevir. Use combination with caution and monitor for dose-related amlodipine toxicity.		In healthy subjects, the kinetics of single dose amlodipine 5 mg/atorvastatin 20 mg (coformulated) were assessed alone and with steady-state telaprevir 750 mg q8h. In the presence of telaprevir, amlodipine Cmax ↑ 27% and AUC ↑ 179%. Monitor for dose-related amlodipine toxicity when coadministering with telaprevir.[45]
Buprenorphine	In HCV-negative volunteers on stable, maintenance		In HCV-negative volunteers on stable, maintenance doses

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	doses (8/2 mg to 24/6 mg QD) of buprenorphine/naloxone, coadministration of boceprevir 800 mg q8h for 6 days did not have a clinically significant impact on the pharmacokinetics of buprenorphine (AUC ↑ 20%, Cmax ↑ 18%) or naloxone (AUC ↑ 30%, Cmax ↑ 9%). Boceprevir exposures in the presence of buprenorphine/naloxone were similar to historical controls. Dose adjustment is likely not necessary when boceprevir is co-administered with buprenorphine/naloxone.[46]		of buprenorphine/naloxone, coadministration of telaprevir 750 mg q8h for 7 days did not have a clinically significant impact on the pharmacokinetics or pharmacodynamic effects of buprenorphine. Telaprevir exposure was consistent with historical control when co-administered with buprenorphine/naloxone. Dose adjustment is not necessary when telaprevir is co-administered with buprenorphine/naloxone.[47]
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.[32]	
Clarithromycin	In healthy subjects, clarithromycin had minimal effects on steady-state BOC exposure. Clarithromycin (in the presence of diflunisal) increased BOC AUC by 21% and Cmax by 36%.[6]		
Corticosteroids (oral/inhaled, injectable or topical) e.g., betamethasone, budesonide, dexamethasone, fluticasone, prednisone, triamcinolone	<u>Inhaled/nasal fluticasone and budesonide</u>: Potential for ↑ corticosteroid concentrations resulting in significantly reduced serum cortisol concentrations. Avoid co-administration if possible, particularly for extended durations.[1] Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest		<u>Inhaled/nasal fluticasone and budesonide</u>: Potential for ↑ corticosteroid concentrations resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.[4] Inhaled beclomethasone or ciclesonide, or intranasal

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	possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[48] Systemic dexamethasone: Potential for ↓ boceprevir concentrations via CYP3A4 induction by dexamethasone. Avoid combination if possible, use with caution if necessary.[1] Prednisone: In healthy volunteers, steady-state boceprevir 800 mg TID did not significantly affect the pharmacokinetics of single-dose prednisone 40 mg (prednisone AUC ↑ 22%, prednisolone AUC ↑ 37%). These results suggest that no dosage adjustment is necessary, but patients should be monitored appropriately for potential toxicities associated with prolonged increases in prednisolone exposure.[49]		beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[48] Systemic dexamethasone: Potential for ↓ telaprevir concentrations via CYP3A4 induction by dexamethasone. Use combination with caution or consider alternate agents.[4]
Daclatasvir	Potential for increased daclatasvir exposures due to CYP3A4 inhibition by boceprevir. Reduce daclatasvir dose to 30 mg once daily when coadministered with boceprevir or other strong inhibitors of CYP3A4.[50]	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.[50]	With coadministration of telaprevir 750 mg q8h and daclatasvir 20 mg daily, daclatasvir AUC increased 115%, Cmax increased 22%, and telaprevir exposures were unchanged. Reduce daclatasvir dose to 30 mg once daily when coadministered with telaprevir or other strong inhibitors of CYP3A4.[50]
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	

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		clinically relevant.[32]	
Digoxin	In an open-label, randomized crossover study, healthy volunteers received single dose digoxin 0.25 mg alone or in combination with multiple-dose boceprevir 800 mg TID. In the presence of boceprevir, digoxin AUC was ↑ 19% and Cmax ↑ 18%, while terminal t½ was unchanged. These results suggest that dosage adjustment of digoxin is not necessary with concomitant boceprevir therapy, and that boceprevir does not appear to exert significant P-gp inhibition at clinically relevant concentrations.[7] Patients receiving treatment with both boceprevir and digoxin should be monitored appropriately.[1]	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.[32]	In an open-label study, healthy subjects received single doses of IV midazolam 0.5 mg, and oral midazolam 2 mg with oral digoxin 0.5 mg administered sequentially alone and in combination with multiple-dose telaprevir 750 mg q8h. In the presence of telaprevir, digoxin Cmax ↑ 50% and AUC ↑ 85%, while renal clearance was not changed.[51] Initiate digoxin at the lowest dose, and monitor serum digoxin concentrations to titrate to desired clinical effect.[4]
Eltrombopag	In healthy volunteers, the pharmacokinetics of single-dose eltrombopag 200 mg given alone or in the presence of steady-state boceprevir 800mg q8h was assessed. Boceprevir Cmax increased 20%, Ctau decreased 32% while AUC was unchanged when coadministered with eltrombopag; eltrombopag pharmacokinetics were not altered in the presence of boceprevir. Dose adjustment is not required when eltrombopag is coadministered with boceprevir.[52]		In healthy volunteers, the pharmacokinetics of single-dose eltrombopag 200 mg given alone or in the presence of steady-state telaprevir 750 mg q8h was assessed. Neither telaprevir nor eltrombopag pharmacokinetics were altered when the drugs were coadministered. Dose adjustment is not required when eltrombopag is coadministered with telaprevir.[52]
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.	

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		Coadministration of simeprevir with moderate-strong 3A4 inhibitors is not recommended.[32]	
Escitalopram	In healthy volunteers, the kinetics of single dose escitalopram 10 mg were not altered to a clinically significant manner in the presence of multiple dose boceprevir 800 mg TID. The pharmacokinetics of boceprevir were similar with and without coadministration of escitalopram. No dosage adjustment is expected to be required with coadministration of this combination.[53]	In healthy subjects, administration of escitalopram 10 mg daily with steady-state simeprevir 150 mg once daily led to 3% ↑ 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.[54]	In healthy volunteers, coadministration of escitalopram 10 mg daily with telaprevir 750 mg q8h for 7 days resulted in 35% ↓ escitalopram AUC, while telaprevir exposures were not affected. May need to titrate escitalopram dose according to clinical response.[55]
HmgCoA reductase inhibitors (statins): atorvastatin lovastatin pravastatin rosuvastatin simvastatin	In healthy volunteers, the kinetics of single dose **atorvastatin 40 mg** in the presence of steady-state BOC 800 mg TID were significantly increased (atorvastatin AUC ↑ 130% and Cmax ↑ 170%) compared to administration alone. BOC kinetics were not significantly affected by atorvastatin coadministration. A lower maintenance dose of atorvastatin may be warranted with concomitant BOC therapy; additional clinical monitoring for symptoms of statin toxicity is recommended if atorvastatin doses of greater than 40 mg daily are used.[56] In healthy volunteers, the kinetics of single dose **pravastatin 40 mg** in the presence of steady-state BOC 800 mg TID were increased (pravastatin AUC ↑ 60% and Cmax ↑ 50%) compared to administration alone. BOC kinetics were	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[32]	In healthy subjects, the kinetics of single dose amlodipine 5 mg/atorvastatin 20 mg (coformulated) were assessed alone and with steady-state telaprevir 750 mg q8h. In the presence of telaprevir, atorvastatin Cmax ↑ 10.6-fold and AUC ↑ 7.88-fold.[45] **Atorvastatin, lovastatin and simvastatin are contraindicated with telaprevir**.[57]

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	not significantly affected by pravastatin coadministration. This slight increase may reflect potential inhibition of OATP by BOC, since pravastatin is not metabolized to a significant extent by CYP450 and is a substrate of OATP1B1 and OATP2B1, but not of P-gp. It is anticipated that pravastatin treatment can be initiated at the recommended dose when co-administered with BOC, with close clinical monitoring.[56] **Lovastatin and simvastatin are contraindicated with boceprevir**.[57]		
Ketoconazole	In healthy subjects, ketoconazole (KCZ) increased BOC AUC ↑131%, Cmax ↑ 41%.[6] When coadministration is required, doses of ketoconazole and itraconazole should not exceed 200 mg/day.[1]	Coadministration of simeprevir with moderate-strong 3A4 inhibitors is not recommended.[32]	In healthy subjects, the effect of single dose ketoconazole 400 mg on the kinetics of single dose (750 mg) or multiple dose (750 mg q8h) telaprevir was studied. When single doses of both drugs were coadministered, telaprevir Cmax ↑ 24% and AUC ↑ 62%. However, after multiple doses of telaprevir, there was no discernible effect of ketoconazole on telaprevir exposure. High (>200 mg per day) doses of ketoconazole or itraconazole are not recommended with telaprevir.[31]
Levothyroxine			In a case series of 4 patients with hypothyroidism treated with levothyroxine, a sharp rise in TSH was observed after initiating therapy with telaprevir, ribavirin, and peg interferon-alpha 2a. TSH elevations persisted despite increases in levothyroxine dosages and administration of levothyroxine on an empty stomach at least 2 hours before any food or

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			medications. TSH levels rapidly returned to baseline once telaprevir was discontinued. Possible explanations for this effect include protein-binding competition between telaprevir and hormone, a change in T4 metabolism, a decrease in T4 production, or a decreased conversion of T4 to T3.[58]
Methadone	In HCV-negative volunteers on stable, maintenance doses (20-150 mg QD) of methadone, boceprevir 800 mg q8h was coadministered for 6 days. In the presence of boceprevir, exposures of R-methadone were decreased (AUC ↓ 16%, Cmax ↓ 10%) and S-methadone were decreased (AUC ↓ 22%, Cmax ↓ 17%). These changes did not result in clinically significant effects including withdrawal. Boceprevir exposures in the presence of methadone were similar to historical controls. Dose adjustment is likely not necessary when boceprevir is co-administered with methadone.[46] Clinical monitoring is recommended, with dose adjustments of methadone if necessary during concomitant treatment with boceprevir.[1]	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.[59]	In HCV-negative volunteers on stable methadone maintenance therapy (median methadone dose 85 mg, range 40-120 mg/day), telaprevir 750 mg q8h was co-administered for 7 days. In the presence of telaprevir, R-methadone Cmin ↓ 31%, Cmax ↓ 21% and AUC ↓ 21%. The AUC ratio of S-/R-methadone was comparable before and during coadministration of telaprevir. The median unbound fraction of R-methadone ↑ from 7.92% to 9.98% during coadministration with telaprevir, but the median unbound Cmin of R-methadone was similar before and during telaprevir coadministration. A priori methadone dose adjustments are not required when initiating telaprevir, but close monitoring is recommended, with dose adjustments if necessary.[60]
NSAIDS	In healthy subjects, co-administration of diflunisal or ibuprofen (aldo ketoreductase inhibitors) had little effect on the steady-state exposure to BOC.[6]		
Oral contraceptives	In healthy subjects, there were no clinically relevant changes in BOC exposure	In healthy female volunteers, no clinically relevant changes in the pharmacokinetics of	In healthy women receiving Modicon (0.5 mg norethindrone (NE) and 0.035

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	when co-administered with drospirenone (DRSP) 3 mg/ethinyl estradiol (EE) 20 ug. BOC increased DRSP $AUC_{(0-24h)}$ and C_{max} (99% and 57%, respectively); and decreased EE AUC (24%) with no effect on EE $C_{max.}$.[6] Alternative methods of non-hormonal contraception are recommended. Co-administration of BOC with drospirenone (Yaz®, Yasmin®, Angeliq®) is contraindicated.[1] In healthy women, coadministration of boceprevir 800 mg TID with ethinyl estradiol (EE) 0.035 mg/norethindrone (NE)1 mg resulted in 26% ↓ AUC, 21% ↓ Cmax of EE and 17% ↓ Cmax of NE. However, based FSH, LH, SHBG, and progesterone levels, these changes are not considered clinically significant and coadministration of boceprevir with EE/NE is unlikely to alter the effectiveness of the combined oral contraceptive Ortho-Novum® 1/35.[61]	ethinyl estradiol and norethindrone were observed when coadministered with simeprevir 150 mg daily for 10 days. Systemic hormonal contraceptives may be used with simeprevir.[62]	mg ethinyl estradiol (EE) for at least 3 months, the effect of steady-state telaprevir 750 mg q8h on the steady-state pharmacokinetics of EE and NE was assessed. In the presence of telaprevir, EE Cmax ↓ 26%, Cmin ↓ 37% and AUC ↓ 28%. NE and telaprevir exposures were not significantly affected. LH and FSH concentrations at day 7 also ↑, corresponding with the ↓ EE concentrations. **Alternative methods of contraception should be used when estrogen-based contraceptives are coadministered with telaprevir**.[63]
Pegylated interferon alfa-2b	In healthy subjects, there were no clinically relevant changes in either BOC or PEG2b exposure when co-administered with pegylated interferon alfa-2b. No BOC dosage adjustment is needed with co-administration.[6]		
Phosphodiester-ase Type 5 (PDE5) Inhibitors • **sildenafil** (Viagra®, Revatio®); *(CYP3A4>>2C9*	↑ in PDE-5 inhibitor concentrations are expected, and may result in an increase in adverse effects, including hypotension, syncope, visual disturbances, and priapism.		↑ in PDE-5 inhibitor concentrations are expected, and may result in an increase in adverse effects. **<u>For treatment of pulmonary</u>**

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substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions) • **tadalafil** (Cialis®, Adcirca®); *CYP3A4 substrate* • **vardenafil** (Levitra®); substrate of *CYP3A4>3A5, 2C*	**For treatment of pulmonary arterial hypertension (PAH):**[1] • **Sildenafil or tadalafil use for PAH is contraindicated with boceprevir.** **For treatment of erectile dysfunction:** Use with caution and increased monitoring for PDE-5 inhibitor-associated toxicities. Do not exceed the following doses:[1] • sildenafil: 25 mg every 48 hours • tadalafil: 10 mg every 72 hours • vardenafil: 2.5 mg every 24 hours (NB: this dose not approved in Canada; therefore, combination is not recommended)		**arterial hypertension (PAH):**[4] • **Sildenafil use for PAH is (contraindicated with telaprevir.** • Co-administration of tadalafil and telaprevir for PAH treatment is not recommended. **For treatment of erectile dysfunction:** Use with caution and increased monitoring for PDE-5 inhibitor-associated toxicities. Do not exceed the following doses:[4] • sildenafil: 25 mg every 48 hours • tadalafil: 10 mg every 72 hours • vardenafil: **contraindicated**
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.	In healthy volunteers administered boceprevir 800 mg TID or omeprazole 40 mg QD alone or in combination, no clinically significant changes in pharmacokinetics were noted with either drug. Boceprevir and omeprazole may be coadministered without dose adjustment.[64]	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.[32]	
Ribavirin			Ribavirin pharmacokinetics were determined in 21 HCV-infected subjects, 16 on pegylated interferon/ribavirin (PR) alone, and 5 on telaprevir/PR. Dose-adjusted ribavirin plasma AUC was 1.54-fold higher in those receiving telaprevir/PR vs PR alone (p=0.002). Ribavirin mono-, di- and tri-phosphate in red blood cells were 3.3, 2.3, and 2.4-fold higher in those on telaprevir/PR

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			compared to those on PR alone; similarly, ribavirin mono-, di- and tri-phosphate in PBMC were 2.5, 3, and 2-fold higher in those on telaprevir/PR compared to those on PR alone (all statistically significant). In patients on telaprevir/PR, intracellular ribavirin concentrations declined after stopping telaprevir. Besides telaprevir use, no other variables including Clcr, age, gender or race were associated with plasma or intracellular ribavirin pharmacokinetics. Increased ribavirin concentrations due to telaprevir coadministration may possibly be a factor in the increased rates of anemia observed with triple therapy.[65]
Rifampin	Coadministration is contraindicated, as boceprevir concentrations may be significantly reduced, possibly leading to decreased virologic response.[1]	In healthy subjects, administration of rifampin 600 mg daily with steady-state simeprevir 200 mg 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.[10] Coadministration of simeprevir with moderate-strong 3A4 inducers is not recommended.[32]	In healthy subjects, coadministration of rifampin 600 mg daily at steady-state and single dose telaprevir 750 mg led to 86% ↓ Cmax and 92% ↓ AUC of telaprevir. Coadministration of rifampin and telaprevir is contraindicated.[31]
Warfarin	Combination has not been studied. Potential for altered warfarin concentrations in the presence of boceprevir. Monitor INR when coadministering warfarin and boceprevir.[1]	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.[32]	In vitro, the effect of 14C-telaprevir at various concentrations on the protein-binding of 3H-warfarin was evaluated in human plasma. Protein-binding of 14C-telaprevir in human plasma was 59.1-75.6% over the concentration range of 0.1 to 20 uM. The free fraction of 14C-telaprevir ↑ ~30% in the presence of warfarin at low 14C-telaprevir concentrations,

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			but this was not observed at high 14C-telaprevir doses. Protein binding of 3H-warfarin in human plasma was 98% and was unchanged by the presence of telaprevir over the concentration range of 0.1 to 20 uM. At low 14C-telaprevir concentrations, warfarin and other ligands with high affinity binding to albumin or alpha1-acid glycoprotein may displace 14C-telaprevir from protein binding sites and ↑ the free fraction of telaprevir.[66] Case report of a 45 yo Hispanic man maintained on warfarin 6 mg daily for 8 months with therapeutic INRs (2.5-3.5). The patient initiated triple therapy with ribavirin, pegylated-interferon and telaprevir, and two days later had an INR of 6.0. He then missed five consecutive warfarin doses, resulting in a below-target INR. An increase in the weekly warfarin dose of 50% above the baseline dose (i.e., 9 mg daily) was required to re-attain a target INR. The warfarin dosing requirement began to decline only after the man finished the prescribed 12-week course of telaprevir. The warfarin dosage needed to maintain a target INR fell to nearly its baseline level after telaprevir was completed.[67] Monitor INR when coadministering warfarin and telaprevir.[4]

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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