Interactions between Directly Acting Antivirals and Drugs for Treatment of Pulmonary Arterial Hypertension (PAH)

	Boceprevir	Telaprevir
Prostaglandin (prostacyclin) analogs		
Epoprostenol (IV) • *Undergoes rapid hydrolyzation* Treprostinil (IV or SC infusion) • *substantially metabolized by the liver, but precise enzymes unknown* • *does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A* Iloprost (inhalation) • *CYP enzymes play minor role in biotransformation; iloprost does not inhibit CYP450 system (in vitro)*	Significant pharmacokinetic interactions with directly acting antiviral agents are not anticipated.	
Endothelin receptor antagonists		
Ambrisentan (Volibris®) • *substrate of UGT1A9S, 2B7S, and 1A3S, CYP3A4 and CYP2C19, OATP, and P-gp.* • *does not inhibit UGT1A1, UGT1A6, UGT1A9, UGT2B7 or CYP450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Additional in vitro studies showed that ambrisentan does not inhibit P-gp, NTCP, OATP or BSEP. Furthermore, ambrisentan does not induce MRP2, P-gp or BSEP.*	Potential for ↑ ambrisentan concentrations with concomitant CYP3A4 inhibitors. Monitor for ambrisentan toxicity.	Case report of a 58 year old HBV/HCV/HIV coinfected male with PAH stabilized on bosentan 125 mg BID who experienced neuropsychiatric adverse effects, elevated AST and ALT and 4-fold ↑ bosentan exposures 17 days after the initiation of telaprevir treatment. HCV and PAH treatments were stopped, and the patient's symptoms quickly resolved Three months later, ambrisentan 5 mg daily was started and telaprevir treatment was resumed, with no adverse effects noted.[1]
Bosentan (Tracleer®) • *substrate of CYP2C9 and CYP3A* • *inducer of CYP2C9 and CYP3A4.*[2, 3]	Potential for ↑ bosentan concentrations with coadministration. Use combination with caution and monitor for bosentan toxicity.[4] Theoretical potential for ↓ boceprevir concentrations with coadministration via enzyme induction (clinical significance unknown). Monitor for boceprevir efficacy.	Case report of a 58 year old HBV/HCV/HIV coinfected male with PAH stabilized on bosentan 125 mg BID who experienced neuropsychiatric adverse effects, elevated AST and ALT and 4-fold ↑ bosentan exposures 17 days after the initiation of telaprevir treatment. HCV and PAH treatments were stopped, and the patient's symptoms quickly resolved Three months later, ambrisentan 5 mg daily was started and telaprevir treatment was resumed, with no adverse effects noted.[1]

	Boceprevir	Telaprevir
Phosphodiesterase inhibitors		
Sildenafil (Revatio®) • *CYP3A4>>2C9 substrate; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions*	**Sildenafil use for PAH is contraindicated with boceprevir.**[4]	**Sildenafil use for PAH is contraindicated with telaprevir.**[5]
Tadalafil (Adcirca®) • *CYP3A4 substrate*	**Tadalafil use for PAH is contraindicated with boceprevir.**[4]	Co-administration of tadalafil and telaprevir for PAH treatment is not recommended.[5]

References:

1. Le MP, Gervais A, Le Beller C, et al. Serious neuropsychiatric adverse effects in a hepatitis C virus/hepatitis B virus/HIV-coinfected patient receiving bosentan and telaprevir. J Antimicrob Chemother 2013;[epub ahead of print, January 13].

2. Acetelion Pharmaceuticals Ltd. Tracleer (bosentan) Product Monograph. Laval, QC June 27, 2011.

3. Weiss J, Herzog M, Haefeli WE. Differential modulation of the expression of important drug metabolising enzymes and transporters by endothelin-1 receptor antagonists ambrisentan and bosentan in vitro. Eur J Clin Pharmacol 2011;660(2-3):298-304.

4. Merck Canada Inc. Victrelis (boceprevir) Product Monograph. Kirkland, QC May 13, 2013.

5. Vertex Pharmaceuticals Inc. Incivek (telaprevir) Product Monograph. Laval, QC February 20, 2013.