

Drug Interactions Between Directly Acting Antivirals (DAAs) and Benzodiazepines

Drug (route of metabolism)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Simeprevir (GALEXOS®, SMV, TMC435) Janssen	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals
Lorazepam, oxazepam, temazepam (UGT)	No interaction expected based on known pharmacologic characteristics. Preferred agents due to lower interaction potential with DAAs. Monitor and titrate dose according to clinical response.	No interaction expected based on known pharmacologic characteristics. Preferred agents due to lower interaction potential with DAAs. Monitor and titrate dose according to clinical response.	No interaction expected based on known pharmacologic characteristics. Preferred agents due to lower interaction potential with DAAs. Monitor and titrate dose according to clinical response.
Alprazolam (CYP3A4)	No interaction studies have been done with intravenous benzodiazepines. Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of boceprevir with intravenous benzodiazepines (alprazolam, midazolam, triazolam) . Dose adjustment of the benzodiazepine should be considered. ¹	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	In healthy subjects who received a single dose of alprazolam 0.5 mg alone and in combination with multiple doses of telaprevir 750 mg po q8h, alprazolam AUC ↑ 35% and the mean t1/2 increased from 13.4 hours to 18.7 hours in the presence of telaprevir. ²
Buspirone (CYP3A4)	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.
Diazepam (CYP2C19>3A)	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider starting with a decreased benzodiazepine dose or select an alternate agent such as lorazepam, oxazepam or temazepam.	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider starting with a decreased benzodiazepine dose or select an alternate agent such as lorazepam, oxazepam or temazepam.

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Midazolam – oral (CYP3A4)	In healthy subjects, coadministration of oral midazolam plus steady-state BOC resulted in increased MDZ exposure: 177% ↑ C ₃ ^{max} and 430% ↑ AUC _{0-24 h} . Boceprevir is contraindicated with oral midazolam. ¹	In healthy subjects, administration of single dose oral or IV midazolam in the presence of steady-state simeprevir 150 mg once daily led to 45% ↑ and 10% ↑ AUC midazolam, respectively. This demonstrates that simeprevir exhibits clinically relevant CYP3A4 inhibition in the intestine (with po midazolam) but not in the liver (with IV midazolam). ⁴	In an open-label study, healthy subjects received single doses of IV midazolam 0.5 mg, and oral midazolam 2 mg administered sequentially alone and in combination with multiple-dose telaprevir 750 mg q8h. In the presence of telaprevir, midazolam oral C _{max} ↑ 2.86-fold and AUC ↑ 8.96-fold. ⁵ Telaprevir is contraindicated with oral midazolam. ⁶
Midazolam – IV (CYP3A4)	No interaction studies have been done with intravenous benzodiazepines. Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of boceprevir with intravenous benzodiazepines (alprazolam, midazolam, triazolam) . Dose adjustment of the benzodiazepine should be considered. ¹	In healthy subjects, administration of single dose oral or IV midazolam in the presence of steady-state simeprevir 150 mg once daily led to 45% ↑ and 10% ↑ AUC midazolam, respectively. This demonstrates that simeprevir exhibits clinically relevant CYP3A4 inhibition in the intestine (with po midazolam) but not in the liver (with IV midazolam). ⁴	In an open-label study, healthy subjects received single doses of IV midazolam 0.5 mg administered sequentially alone and in combination with multiple-dose telaprevir 750 mg q8h. In the presence of telaprevir, midazolam IV AUC ↑ 3.4 fold. ⁵ Co-administration of telaprevir and parenteral midazolam should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. ⁶
Triazolam (CYP3A4)	Potential for ↑ benzodiazepine concentrations ¹	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	Triazolam is contraindicated with boceprevir and telaprevir. ^{1,6}
Zolpidem (CYP3A)	Potential for ↑/↓	Potential for ↑	Use combination with

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>> 2C9, 1A2 >> 2D6, 2C19)	benzodiazepine concentrations. In healthy subjects who received a single dose of zolpidem 5 mg alone and in combination with a single 750 mg telaprevir dose and multiple telaprevir doses of 750 mg po q8h, zolpidem exposures were unchanged after single dose telaprevir, while zolpidem C _{max} ↓ 42% and AUC ↓ 47% after steady-state dosing of telaprevir. The mean t _{1/2} of zolpidem decreased from 4.32 hours to 3.37 hours following multiple doses of telaprevir. ²	benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	caution, and monitor for benzodiazepine-related efficacy or toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam. Clinical monitoring and dose titration of zolpidem is recommended to achieve the desired clinical response when coadministering with telaprevir.
Zopiclone (CYP3A4> 2C8, 2C9)	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.	Potential for ↑ benzodiazepine concentrations. Use combination with caution, and monitor for benzodiazepine-related toxicity. Consider an alternate agent such as lorazepam, oxazepam or temazepam.

Legend: CYP = cytochrome P450, P-gp = p-glycoprotein, UGT = Uridine 5'-diphospho-glucuronosyltransferases

References:

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