Review

Carboxylesterase Factors Influencing the Therapeutic Activity of Common Antiviral Medications Used for SARS-CoV-2 Infection

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Table S1. CES-mediated activation of antiviral drugs and potential drug-drug interactions

Antivirals	Activation Pathway	Broader Activation Pathway Involved Other Enzymes/Transporters	Clinical Implications and Potential Drug-Drug Interactions
Veklury® (Remdesivir)	Hydrolyzed by CES1 → active nucleotide analog (phosphorylation/dephosphorylation)	• hydrolyzed by Cathepsin A • oxidized by CYP3A4, CYP2B6, CYP2C8, CYP2D6 • transported by ENT and CNT • inhibits CES2 irreversibly at low concentrations • kinases and phosphatases can active/inactive drug by phosphorylating/dephosphorylating	• CYP interactions, particularly interactions with CYP3A4 inhibitors/inducers • affect CES2 substrates • caution with co-administering drugs that affect kinase/ phosphatase activity
LAGEVRIO™ (Molnupiravir)	Hydrolyzed by CES2 → active nucleotide analog (phosphorylation/dephosphorylation)	• oxidized by CYP but minor CYP involvement. • transported by ENT and CNT but less dependent on transporters compared to remdesivir. • kinases and phosphatases can active/inactive drug by phosphorylating/dephosphorylating	• lower CYP interaction risks compared to remdesivir • activation impaired by CES2 inhibitors • caution with co-administering drugs that affect kinase/ phosphatase activity
Paxlovid™ (Nirmatrelvir/Ritonavir)	-	nirmatrelvir: • oxidized by CYP, particularly CYP3A4 • inhibits OATP 1A2, 1B1, 1B3, and 2B1 at high concentrations ritonavir: • inhibits CYP and P-gp	• High potential of CYP interaction, particularly CYP3A subtrates