

## Drug Interactions with nirmatrelvir-ritonavir (Paxlovid®)

Nirmatrelvir-ritonavir is a combination medicine used to treat COVID-19 infections. Ritonavir increases (boosts) the concentration of nirmatrelvir by inhibiting its clearance by CYP3A enzymes. This also increases the concentration of other drugs metabolised by CYP3A. This is why drug interactions are a 'problem' for some patients. The interactions of greatest concern are with narrow therapeutic index medicines metabolised by CYP3A.

### Narrow therapeutic index medicines metabolised by CYP3A

Anticoagulants	rivaroxaban, warfarin (R-warfarin)
Anticonvulsants	carbamazepine
Antineoplastic agents	docetaxel, irinotecan, paclitaxel, vinblastine, vincristine
Benzodiazepines +	clonazepam, diazepam, midazolam and zopiclone
Immunosuppressants	ciclosporin, everolimus, sirolimus, tacrolimus
Opioids	fentanyl, oxycodone

For these medicines withholding is often not an option. If the medicine needs to be continued the options are:

- use remdesivir (*or molnupiravir*) as an alternative to nirmatrelvir-ritonavir, or
- reduce the dose of the affected medicine for the 5 days of nirmatrelvir-ritonavir treatment and monitor more closely, e.g. INR for warfarin.

Nirmatrelvir is metabolised by CYP3A and major inducers of this enzyme (below) are likely to make the treatment ineffective. For these patients use remdesivir (*or molnupiravir*).

### Strong CYP3A inducers

carbamazepine, phenytoin, rifampicin, St John's wort

Nirmatrelvir-ritonavir for the treatment of COVID-19 is a 5 day course. Hence, the clinical significance of drug interactions with ritonavir is less than with the longer courses required for HIV. There are four ways to minimise the risk of adverse effects from a drug interaction with CYP3A substrates:

1. Withhold the affected medicine while taking nirmatrelvir-ritonavir (for 5 days).  
e.g. for simvastatin and atorvastatin.
2. Continue the affected medicine while taking nirmatrelvir-ritonavir, caution the patient and monitor for adverse effects.  
e.g. hypotension with calcium channel blockers.
3. Reduce the dose (amount or frequency) of the affected medicine while taking nirmatrelvir-ritonavir and monitor.  
e.g. tacrolimus concentration, INR for warfarin.
4. Use remdesivir (*or molnupiravir*) instead of nirmatrelvir-ritonavir.

### CYP3A substrates

Gastrointestinal System	domperidone, loperamide
Cardiovascular System	amiodarone, amlodipine, apixaban, atorvastatin, bezafibrate, diltiazem, doxazosin, felodipine, nifedipine, propranolol, quinine, rivaroxaban, simvastatin, sildenafil, tadalafil, ticagrelor, vardenafil, verapamil
Respiratory System	chlorpheniramine, loratadine
Central Nervous System	alprazolam, aprepitant, aripiprazole, buspirone, carbamazepine, clonazepam, diazepam, fentanyl, galantamine, haloperidol, methadone, midazolam, pimozide, quetiapine, risperidone, triazolam, ziprasidone
Infections	boceprevir, clarithromycin, dapsone, erythromycin, indinavir, itraconazole, ketoconazole, nelfinavir, nevirapine, roxithromycin, saquinavir, telaprevir, voriconazole
Endocrine System	dexamethasone, finasteride, fludrocortisone, methylprednisolone
Malignant Disease and Immunosuppression	ciclosporin, docetaxel, everolimus, flutamide, imatinib, irinotecan, paclitaxel, sirolimus, sorafenib, tacrolimus, vinblastine, vincristine
Anaesthesia	lidocaine

### General

- Don't change the dose regimen of nirmatrelvir-ritonavir.
- If doses of the patient's other medicines are reduced, resume previous doses of the patients other medicines on completion of the course. CYP3A inhibition by ritonavir resolves within 3 days of stopping.
- The interaction checker in NZF can be used. However, some of the interactions identified are not clinically relevant. If you are not sure get advice.
- The lists in the tables above are not exhaustive.

Prescriber information on nirmatrelvir-ritonavir is [available in the NZF](#).

Patient information for nirmatrelvir-ritonavir is [available in MyMedicines](#).

**If you are not sure** discuss the patient with the physician or service involved in that aspect of their care, or contact the medicines information service 03 364 0900.