Christchurch Medicines Information Service
August 2022 (last updated: 12 August 2022 at 5pm)

Clinical Pharmacology

Te Whatu Ora Health New Zealand Waitaha Canterbury

medicines.information@cdhb.health.nz 03 364 0900 medicinesinformation.co.nz

Drug Interactions with nirmatrelvir-ritonavir (Paxlovid®)

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. The tables below provide guidance on adjusting doses of patients' medicines when treating COVID-19 infection with a 5 day course of nirmatrelvir-ritonavir. There are 4 ways to minimise the risk of adverse effects:

1. Withhold the affected medicine while taking nirmatrelvir-ritonavir (for 5 days).
2. Reduce the dose (amount or frequency) of the affected medicine while taking nirmatrelvir-ritonavir (for 5 days) and monitor.
3. Continue the affected medicine while taking nirmatrelvir-ritonavir, caution the patient and monitor for adverse effects.
4. Use remdesivir (or molnupiravir) instead of nirmatrelvir-ritonavir.

There is no one right approach, dosing decisions need to be individualised and closer monitoring will be indicated for some patients and some medicines not listed below.

Where dose changes are needed, we recommend withholding or reducing the dose of a medicine while taking nirmatrelvir-ritonavir (5 days) and then resuming the usual dose. This is simple for the patient to remember. It is important that patients resume their usual medicines after finishing the course of nirmatrelvir-ritonavir. Some guidelines recommend withholding for longer based on the predicted duration of the inhibitory effects of ritonavir on the CYP3A enzymes. 5 days is sufficient to avoid adverse effects in most circumstances; however, one week is another valid option.

Dose reduction is usually by halving the dose, this is not a precise correction but is sufficient to avoid adverse effects in many cases. To reduce the dose by half, either take every second dose (e.g. if twice daily then take once daily, or if once daily then take every second day) or the dose amount can be halved (e.g. halve the tablet, if not controlled release). Whichever is the easiest or most practical for the patient.

If in doubt discuss the patient with others involved in their care and/or seek advice.

Most drug-drug interactions can be safely managed using the following strategies:

Withhold for the duration of nirmatrelvir-ritonavir	
α-blockers	doxazosin, prazosin, terazosin
Benzodiazepines	clonazepam, diazepam, midazolam, triazolam
Calcium channel blockers	amlodipine, felodipine, nifedipine
Statins	atorvastatin, simvastatin
Fibrates	bezafibrate
Urate lowering agents	colchicine

Halve the dose for the duration of nirmatrelvir-ritonavir	
Anticoagulants (oral)	dabigatran etexilate, rivaroxaban, warfarin Monitor INR or TCT and for signs of bleeding and bruising (see below).
Calcium channel blockers	diltiazem, verapamil Monitor for bradycardia and hypotension.
Carbamazepine	Also induces CYP3A which will decrease nirmatrelvir concentrations.
Opioids	fentanyl, oxycodone, pethidine Consider morphine as a safer alternative. Otherwise, the opioid dose can be halved with close monitoring and further dose titration.

We recommend to continue (not withhold) anticoagulant medicines, as COVID-19 infection increases the risk of venous thromboembolism. For high-risk patients additional monitoring may be needed to manage risk.

- For dabigatran, the change in thrombin clotting time (TCT) can be used to monitor patients. A TCT prior to starting or immediately after starting and 3 days later can be used.
- For rivaroxaban, the change in INR can be used to monitor patients. An INR prior to starting or immediately after starting and 3 days later can be used.
- For warfarin, monitor INR every 2 or 3 days.
- INR and TCT test results are rapidly available after testing. Dabigatran and rivaroxaban concentrations can be measured but the result is not available quickly enough for acute decision making.

Seek specific advice	
Antiarrhythmics	amiodarone, flecainide Discuss with the patient's cardiologist. Amiodarone has a long half-life and could be withheld or continued depending on the clinical scenario.
Cytotoxic agents	Concomitant use is high risk for many cytotoxic agents. Contact the treating oncologist BEFORE starting nirmatrelvir-ritonavir.
Immunosuppressants	tacrolimus, ciclosporin Contact the transplant team (or treating specialist for other conditions) BEFORE starting nirmatrelvir-ritonavir.
Phenytoin	Nirmatrelvir may be ineffective, discuss with infectious diseases.
Rifampicin	Nirmatrelvir may be ineffective, discuss with infectious diseases.

Examples of medicines that can be continued at the same dose	
Antiplatelets	aspirin, clopidogrel Reduced effectiveness of clopidogrel (a prodrug) is likely.
Benzodiazepines	lorazepam, oxazepam, temazepam Metabolised by pathways other than CYP3A.
Finasteride	Adverse effects not significantly increased.
Fludrocortisone	Potential for fluid retention.
Hormonal contraceptives	Consider an additional non-hormonal method of contraception. Contraceptive effectiveness is expected to be maintained.
Loratadine	Potential for sedation.
Low molecular weight heparin	Enoxaparin
Morphine, methadone	Metabolised by pathways other than CYP3A.
Pravastatin	Metabolised by pathways other than CYP3A.

General

- Don't change the dose regimen of nirmatrelvir-ritonavir.
- CYP3A inhibition by ritonavir resolves within 3 days of stopping.
- The lists in the tables are not exhaustive. The examples presented have been raised in questions to the medicines information service.
- Patient information for nirmatrelvir-ritonavir is available from MyMedicines.

If this guidance is insufficient to manage interactions for your patient, please contact the Medicines Information Service 03 364 0900.

Bibliography

- FDA Emergency Use Authorisation (EUA) for Paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets. Centre for Drug Evaluation and Research (CDER) review. Available from: https://www.fda.gov/media/155194/download
- Foerster KI, Hermann S, Mikus G, Haefeli WE. Drug-Drug Interactions with Direct Oral Anticoagulants. Clin Pharmacokinet. 2020 Aug;59(8):967–80.
- Hesse LM, von Moltke LL, Greenblatt DJ. Clinically important drug interactions with zopiclone, zolpidem and zaleplon. CNS Drugs. 2003;17(7):513–32.
- Lingineni K, Farhan N, Kim S, Cristofoletti R, Gordon LA, Kumar P, et al. Quantitative Benefit-Risk Assessment of P-gp-Mediated Drug-Drug Interactions of Dabigatran Coadministered With Pharmacokinetic Enhancers in Patients With Renal Impairment. Clin Pharmacol Ther. 2021 Jan;109(1):193–200.
- McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. Clin Infect Dis Off Publ Infect Dis Soc Am. 2003 Aug 15;37(4):476–82.
- Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. Br J Clin Pharmacol. 2013 Sep;76(3):455–66.
- Nieminen TH, Hagelberg NM, Saari TI, et al. Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir. Eur J Clin Pharmacol 2010;66(10):977-85.
- Olkkola KT, Palkama VJ, Neuvonen PJ. Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. Anesthesiology 1999;91:681-85.
- Paxlovid Drug-Drug Interactions [Internet]. COVID-19 Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/
- Sekar V, Tomaka F, Lefebvre E, De Pauw M, Vangeneugden T, van den Brink W, et al. Pharmacokinetic interactions between darunavir/ritonavir and opioid maintenance therapy using methadone or buprenorphine/naloxone. J Clin Pharmacol. 2011 Feb;51(2):271–8.