Interactions with Essential Medicines & Nirmatrelvir/ritonavir (NMV/r)

Please check www.covid19-druginteractions.org for updates.

Interaction tables - refer to page 2 for legend, abbreviations and notes

Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister.
Drug interaction data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.
Management of interactions with nirmatrelvir/ritonavir (Paxlovid) may be complex and full details should be obtained from the website where possible.

Analgesics	
	Codeine
	Diclofenac
☐	Fentanyl
	Hydromorphone
	Ibuprofen
	Mefenamic acid
	Morphine
☐	Oxycodone
	Paracetamol
	Tramadol
Antiarrhythmics	
!	Amiodarone
☐	Digoxin
☐	Lidocaine
Antibacterials	
	Amikacin
	Amoxicillin
	Ampicillin
☐	Bedaquiline
	Cefalexin
	Cefazolin
	Cefixime
	Cefotaxime
	Ceftriaxone
	Chloramphenicol
	Ciprofloxacin
	Clarithromycin (a)
	Clindamycin
	Clofazimine
	Cloxacillin
	Cycloserine
	Dapsone
☐	Delamanid
	Doxycycline
☐	Erythromycin
	Ethambutol
	Ethionamide
	Gentamicin
	Imipenem/cilastatin
	Isoniazid
	Kanamycin
	Levofloxacin
	Linezolid
	Meropenem
	Metronidazole
	Moxifloxacin
	Nitrofurantoin
	Ofloxacin
	Para-aminosalicylic acid
	Penicillins
	Piperacillin
	Pyrazinamide
☐	Rifabutin (b)
✖	Rifampicin
✖	Rifapentine
	Spectinomycin
	Streptomycin
	Sulfadiazine
	Tazobactam
	Tetracyclines
	Trimethoprim/ sulfamethoxazole
	Vancomycin

Anticoagulants/antiplatelets	
☐	Apixaban
	Aspirin (antiplatelet)
	Clopidogrel (stented) (c)
☐	Dabigatran (d)
	Dalteparin
☐	Edoxaban (e)
	Enoxaparin
	Heparin
	Rivaroxaban
	Streptokinase
☐	Warfarin (f)
Anticonvulsants	
✖	Carbamazepine
	Clonazepam
☐	Ethosuximide
	Lamotrigine
✖	Phenobarbital
✖	Phenytoin
	Sodium valproate
	Valproate semisodium (Divalproex sodium)
	Valproic acid
Antidepressants	
	Amitriptyline
	Clomipramine
	Fluoxetine
	Lithium
✖	St John's Wort
Antidiabetics	
	Glibenclamide
	Gliclazide
	Insulin
	Metformin
Antifungals	
	Amphotericin B
	Fluconazole
	Flucytosine
	Griseofulvin
	Itraconazole (g)
	Ketoconazole (g)
	Nystatin
☐	Voriconazole
Antimalarials	
☐	Amodiaquine
	Artemether
	Artesunate
	Atovaquone
	Lumefantrine
☐	Mefloquine
☐	Piperaquine
	Primaquine
	Proguanil
☐	Quinine
Antipsychotics	
	Chlorpromazine
	Clozapine
	Fluphenazine
☐	Haloperidol
☐	Risperidone

Anxiolytics	
	Diazepam
	Lorazepam
	Midazolam
Beta blockers	
	Atenolol
	Bisoprolol
	Carvedilol
	Metoprolol
	Propranolol
Bronchodilators	
	Aminophylline
	Ipratropium bromide
	Salmeterol
Calcium channel blockers	
	Amlodipine
	Nifedipine
	Verapamil
Cancer drugs	
☐	Dasatinib (h)
☐	Erlotinib (i)
	Hydroxycarbamide (Hydroxyurea)
☐	Imatinib (j)
	Methotrexate
	Paclitaxel
	Tamoxifen
☐	Vinblastine (k)
Contraceptives	
	Ethinylestradiol
	Etonogestrel (IMP)
	Etonogestrel (VR)
	Levonorgestrel (COC)
	Levonorgestrel (EC)
	Levonorgestrel (IUD)
	Levonorgestrel (POP)
	Medroxyprogesterone (depot injection)
	Norethisterone (COC)
	Norethisterone (IM)
	Norethisterone (POP)
	Norgestrel (COC)
COVID19 therapies	
	Budesonide (inhaled)
	Convalescent plasma
	Dexamethasone
	Hydrocortisone
	Infliximab
	Methylprednisolone
	COVID19 vaccines
Gastrointestinal agents	
☐	Aprepitant
	Domperidone
	Lactulose
	Loperamide
	Mesalazine
	Metoclopramide
	Omeprazole
	Ondansetron
	Ranitidine
	Senna

HCV antivirals	
	Glecaprevir/pibrentasvir
	Ledipasvir/sofosbuvir
	Ombitasvir/paritaprevir/r
	Sofosbuvir/velpatasvir
Herbals/supplements/vitamins	
	Folic acid
	Iodine
	Magnesium
	Phytomenadione (Vitamin K)
	Pyridoxine (Vitamin B6)
	Retinol (Vitamin A)
	Thiamine (Vitamin B1)
✖	St John's Wort
HIV antiretrovirals	
	Abacavir
	Atazanavir/ritonavir
	Darunavir/ritonavir
	Dolutegravir
	Efavirenz
	Emtricitabine
	Lamivudine
	Lopinavir/ritonavir
	Nevirapine
	Raltegravir
	Tenofovir alafenamide
	Tenofovir-DF
	Zidovudine
Hypertension/heart failure	
	Amiloride
	Dopamine
	Enalapril
	Furosemide
	Hydrochlorothiazide
	Isosorbide dinitrate
	Lisinopril
	Losartan
	Methyldopa
	Spironolactone
Immunosuppressants	
	Azathioprine
	Ciclosporin (l)
	Everolimus (m)
Lipid lowering agents	
☐	Atorvastatin
	Fluvastatin
	Lovastatin
	Simvastatin
Others	
	Allopurinol
	Carbimazole
	Ergometrine
	Ergotamine
	Levodopa
	Levothyroxine
Steroids	
	Beclometasone
	Betamethasone
	Fludrocortisone
	Prednisolone
	Testosterone
☐	Triamcinolone

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Legend

Colour/Symbol		Recommendation for NMV/r use
!	**Do not co-administer**	**Do not use NMV/r ⇒ alternative COVID-19 therapy** Risk of serious toxicity. Stopping the drug does not mitigate the interaction due to its prolonged half-life.
✖	**Do not co-administer**	**Do not use NMV/r ⇒ alternative COVID-19 therapy** Strong inducer can jeopardize NMV/r efficacy due to persisting induction after stopping the drug.
	Do not co-administer	**NMV/r use ONLY possible if drug is paused or replaced by a non-interacting drug** Risk of serious toxicity. Only start NMV/r if the drug can be safely paused or replaced. Drug can be resumed at least 3 days (if possible, up to 5 days for narrow therapeutic index drugs) after completing NMV/r therapy.
☐	**Potential interaction** Dose adjustment and/or close monitoring required.	**Stop or replace drug if possible or consult specialist for dose adjustment/monitoring to allow use with NMV/r** Ideally, only start NMV/r if the drug can be safely paused or replaced. Alternatively, dose adjust/monitor. Refer to www.covid19-druginteractions.org for detailed information.
	Potential interaction Manageable by counselling patient	**Proceed with NMV/r** Interaction manageable by counselling the patient about potential interaction and advising to temporarily stop the drug if feeling unwell.
	Weak interaction No action needed	**Proceed with NMV/r** Drug metabolized partially by CYP3A4 or with low risk of adverse event from interaction.
	No interaction expected	**Proceed with NMV/r**

Contraceptive Abbreviations

COC = combined oral contraceptive
EC = emergency contraception
IUD = intrauterine device
IM = intramuscular
IMP = implant
POP = progestin only contraceptive pill
VR = vaginal ring

Notes

a No dose reduction or monitoring in patients with normal renal function.

b Rifabutin dosed 150 mg once daily with NMV/r.

c Ritonavir decreases clopidogrel efficacy therefore NMV/r cannot be prescribed in high risk situation (i.e. initial period (at least 6 weeks) post coronary stenting). NMV/r is allowed if clopidogrel is used outside this period or if clopidogrel is used as alternative to aspirin (intolerant patients).

d When used for the treatment of atrial fibrillation, reduce dabigatran to 110 mg twice daily in individuals with normal renal function and to 75 mg twice daily in individuals with moderate renal impairment. Consult www.covid19-druginteractions.org for management in other indications.

e When used for the treatment of atrial fibrillation, reduce edoxaban to 30 mg. Consult www.covid19-druginteractions.org for management in other indications.

f Monitor INR as clinically indicated.

g Itraconazole or ketoconazole should not be used at doses >200 mg/day.

h The decision to pause or dose adjust dasatinib should be made in conjunction with the patient's oncologist.
Chronic phase chronic myelogenous leukaemia: pause dasatinib and restart 3 days after completing NMV/r. Alternatively, consider reducing dasatinib dose to 20 mg (in patients receiving 100 mg daily) or 40 mg (in patients receiving 140 mg daily) and monitor for toxicity.
Accelerated or blast phase chronic myelogenous leukaemia: do not coadminister, use alternative COVID-19 therapy.

i The decision to pause or dose adjust erlotinib should be made in conjunction with the patient's oncologist.
If it is decided to pause treatment, restart erlotinib 3 days after completing NMV/r treatment. If pausing erlotinib treatment is not feasible, continue full dose erlotinib with patient self-monitoring for rash and diarrhoea. If these do occur, reduce erlotinib dose in 50 mg decrements or re-assess for a short pause.

j The decision to pause imatinib should be made in conjunction with the patient's oncologist. If it is decided to hold treatment, restart imatinib 3 days after completing NMV/r treatment. Alternatively, imatinib may be coadministered with monitoring for adverse effects (fluid retention, nausea and neutropenia). NMV/r is expected to have a modest effect on imatinib exposure. Coadministration with ritonavir (600 mg once daily) for 3 days did not significantly alter imatinib exposure (*van Erp NP et al. Clin Cancer Res. 2007;13(24):7394-400*).

k The decision to pause or dose adjust vinblastine should be made in conjunction with the patient's oncologist. Vinblastine may be paused in the context of acute infection. Restart vinblastine 3 days after completing NMV/r treatment. Alternatively, vinblastine may be coadministered with close monitoring for haematologic toxicity and neurotoxicity. Some providers may wish to empirically reduce vinblastine dose, especially in patients who have previously experienced or are at high risk for toxicity.

l Management of this interaction is challenging and would require dosage adjustment and TDM of ciclosporin which may not be possible given the short duration of NMV/r treatment. An alternative COVID treatment should be considered. However, if TDM is available, an empiric dose reduction of ciclosporin has been suggested (reduce total daily dose by 80% and administer once daily) and start NMV/r 12 hours after the last dose of ciclosporin. Continue at reduced dose during treatment with NMV/r (days 1-5). Ciclosporin concentrations should be assessed on day 6 or 7 and repeated every 2-4 days. If concentrations are supratherapeutic, reduce the current ciclosporin dose. If concentrations are therapeutic, continue the current ciclosporin dose. If concentrations are subtherapeutic, increase the ciclosporin daily dose and consider resumption of twice daily dosing. In all cases, repeat ciclosporin concentration monitoring after 2-4 days and continue to dose adjust accordingly.

m A large increase in everolimus exposure is predicted in presence of NMV/r. Avoid use of NMV/r unless close monitoring of everolimus concentrations is feasible. If coadministered, hold everolimus and start NMV/r 12 hours after the last everolimus dose. Check everolimus concentrations 1-2 days after the last dose of NMV/r. If concentrations are supratherapeutic, continue to hold everolimus and repeat concentration monitoring in 2-4 days to assess resumption. If concentrations are therapeutic/subtherapeutic, resume everolimus at 25-50% of baseline dose. Repeat concentration monitoring every 2-4 days and dose-adjust accordingly.