# Interactions with Outpatient Medicines & Nirmatrelvir/ritonavir (NMV/r)



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

## Interaction tables - refer to page 3 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 | |
|---|---|
| | Aspirin |
| | Buprenorphine |
| | Celecoxib |
| | Codeine |
| | Dextropropoxyphene |
| | Diclofenac |
| ☐ | Fentanyl |
| | Hydromorphone |
| | Ibuprofen |
| | Mefenamic acid |
| | Methadone |
| | Morphine |
| | Naproxen |
| ☐ | Oxycodone |
| | Paracetamol |
| | Pethidine |
| | Tapentadol |
| | Tramadol |
| **Antiarrhythmics** | |
| ! | Amiodarone |
| | Bepridil |
| ☐ | Digoxin |
| | Disopyramide |
| | Dofetilide |
| | Dronedarone |
| | Flecainide |
| ☐ | Lidocaine |
| | Propafenone |
| | Quinidine |
| **Anticoagulants/antiplatelets** | |
| ☐ | Apixaban |
| | Aspirin (antiplatelet) |
| | Clopidogrel (stented) (a) |
| ☐ | Dabigatran (b) |
| | Dalteparin |
| | Dipyridamole |
| ☐ | Edoxaban (c) |
| | Enoxaparin |
| | Heparin |
| ☐ | Phenprocoumon (d) |
| | Prasugrel |
| | Rivaroxaban |
| | Ticagrelor |
| | Tinzaparin |
| ☐ | Warfarin (d) |

| Anticonvulsants | |
|---|---|
| | Brivaracetam |
| ✖ | Carbamazepine |
| | Clonazepam |
| | Eslicarbazepine |
| ☐ | Ethosuximide |
| | Gabapentin |
| | Lacosamide |
| | Lamotrigine |
| | Levetiracetam |
| | Oxcarbazepine |
| ✖ | Phenobarbital |
| ✖ | Phenytoin |
| | Pregabalin |
| ✖ | Primidone |
| | Retigabine |
| | Rufinamide |
| | Sodium valproate |
| ☐ | Tiagabine |
| | Topiramate |
| | Valproate semisodium (Divalproex sodium) |
| | Valproic acid |
| | Vigabatrin |
| | Zonisamide |
| **Antidepressants** | |
| | Agomelatine |
| | Amitriptyline |
| | Bupropion |
| | Citalopram |
| | Clomipramine |
| | Desipramine |
| | Doxepin |
| | Duloxetine |
| | Escitalopram |
| | Fluoxetine |
| | Imipramine |
| | Lithium |
| | Maprotiline |
| | Mianserin |
| | Mirtazapine |
| | Nortriptyline |
| | Paroxetine |
| ☐ | Reboxetine |
| | Sertraline |
| ✖ | St John's Wort |
| ☐ | Trazodone |
| | Venlafaxine |
| | Vortioxetine |

| Antidiabetics | |
|---|---|
| | Acarbose |
| | Canagliflozin |
| | Dapagliflozin |
| | Dulaglutide |
| | Empagliflozin |
| | Exenatide |
| | Glibenclamide |
| | Gliclazide |
| | Glimepiride |
| | Glipizide |
| | Insulin |
| | Linagliptin |
| | Liraglutide |
| | Metformin |
| | Pioglitazone |
| | Rosiglitazone |
| ☐ | Saxagliptin |
| | Sitagliptin |
| | Tolbutamide |
| | Vildagliptin |
| **Antihistamines** | |
| | Cetirizine |
| | Fexofenadine |
| | Loratadine |
| **Antipsychotics** | |
| | Amisulpride |
| ☐ | Aripiprazole |
| | Asenapine |
| | Chlorpromazine |
| | Clozapine |
| | Fluphenazine |
| ☐ | Haloperidol |
| ☐ | Iloperidone |
| | Levomepromazine |
| | Lumateperone |
| | Lurasidone |
| | Olanzapine |
| | Paliperidone |
| | Periciazine |
| | Perphenazine |
| | Pimozide |
| | Pipotiazine |
| | Quetiapine |
| ☐ | Risperidone |
| | Sulpiride |
| | Tiapride |
| | Ziprasidone |

| Anxiolytics | |
|---|---|
| ☐ | Alprazolam |
| | Bromazepam |
| ☐ | Buspirone |
| ☐ | Clobazam |
| | Clorazepate |
| | Diazepam |
| | Estazolam |
| ☐ | Flunitrazepam |
| | Flurazepam |
| | Lorazepam |
| | Lormetazepam |
| | Midazolam |
| | Oxazepam |
| | Temazepam |
| | Triazolam |
| | Zaleplon |
| | Zolpidem |
| | Zopiclone |
| **Beta blockers** | |
| | Atenolol |
| | Bisoprolol |
| | Carvedilol |
| | Metoprolol |
| | Nebivolol |
| | Propranolol |
| | Sotalol |
| | Timolol |
| **Bronchodilators** | |
| | Aclidinium bromide |
| | Aminophylline |
| | Formoterol |
| | Glycopyrronium bromide |
| | Indacaterol |
| | Ipratropium bromide |
| | Montelukast |
| | Olodaterol |
| | Roflumilast |
| | Salbutamol |
| | Salmeterol |
| | Theophylline |
| | Tiotropium bromide |
| | Umeclidinium bromide |
| | Vilanterol |

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| Calcium channel blockers | |
|---|---|
| | Amlodipine |
| | Diltiazem |
| | Felodipine |
| | Nicardipine |
| | Nifedipine |
| | Nitrendipine |
| | Verapamil |
| **Cancer drugs** | |
| ☐ | Abemaciclib (e) |
| | Abiraterone |
| | Acalabrutinib |
| ☐ | Afatinib |
| | Alectinib |
| ✖ | Apalutamide |
| | Atezolizumab |
| | Bosutinib |
| | Capecitabine |
| ☐ | Ceritinib (e) |
| ☐ | Dasatinib (f) |
| ☐ | Encorafenib (e) |
| ✖ | Enzalutamide |
| ☐ | Erlotinib (e) |
| ☐ | Fostamatinib |
| ☐ | Gilteritinib (e) |
| | Ibrutinib (g) |
| ☐ | Imatinib |
| ✖ | Ivosidenib |
| | Lenalidomide |
| | Midostaurin (h) |
| | Neratinib |
| ☐ | Nilotinib (f) |
| ☐ | Olaparib (e) |
| | Osimertinib |
| ☐ | Palbociclib (e) |
| ☐ | Pazopanib (e) |
| | Pomalidomide |
| ☐ | Ribociclib (e) |
| | Sotorasib |
| ☐ | Sunitinib (e) |
| | Tamoxifen |
| | Venetoclax (i) |
| ☐ | Vinblastine (e) |
| ☐ | Vincristine (e) |
| **Contraceptives** | |
| | Desogestrel (COC) |
| | Desogestrel (POP) |
| | Ethinylestradiol |
| | Etonogestrel (IMP) |
| | Etonogestrel (VR) |
| | Levonorgestrel (COC) |
| | Levonorgestrel (IUD) |
| | Levonorgestrel (POP) |
| | Medroxyprogesterone (depot injection) |
| | Norethisterone (COC) |
| | Norethisterone (IM) |
| | Norethisterone (POP) |
| | Norgestrel (COC) |

| Cystic fibrosis agents | |
|---|---|
| ☐ | Ivacaftor |
| ✖ | Ivacaftor/lumacaftor |
| ☐ | Ivacaftor/tezacaftor |
| ☐ | Ivacaftor/tezacaftor/ elexacaftor |
| **Gastrointestinal agents** | |
| | Antacids |
| | Cisapride |
| ☐ | Aprepitant |
| | Domperidone |
| | Esomeprazole |
| | Famotidine |
| | Lansoprazole |
| | Loperamide |
| | Mesalazine |
| | Metoclopramide |
| | Omeprazole |
| | Ondansetron |
| | Pantoprazole |
| | Rabeprazole |
| | Ranitidine |
| | Senna |
| **HCV antivirals** | |
| | Elbasvir/grazoprevir |
| | Glecaprevir/pibrentasvir |
| | Ledipasvir/sofosbuvir |
| | Sofosbuvir/velpatasvir |
| ☐ | Sofosbuvir/velpatasvir/ voxilaprevir |
| **HIV antiretrovirals** | |
| | Abacavir |
| | Atazanavir/ritonavir |
| | Bictegravir |
| | Cabotegravir |
| | Cabotegravir/rilpivirine (long acting) |
| | Darunavir/ritonavir |
| | Dolutegravir |
| | Doravirine |
| | Efavirenz |
| | Emtricitabine |
| | Etravirine |
| | Fostemsavir |
| | Lamivudine |
| | Nevirapine |
| | Raltegravir |
| | Rilpivirine |
| | Tenofovir alafenamide |
| | Tenofovir-DF |

| Hypertension/heart failure | |
|---|---|
| | Aliskiren |
| | Ambrisentan |
| | Amiloride |
| | Bosentan |
| | Candesartan |
| | Captopril |
| | Cilazapril |
| | Doxazosin |
| | Enalapril |
| | Eplerenone |
| | Eprosartan |
| | Fosinopril |
| | Furosemide |
| | Hydralazine |
| | Hydrochlorothiazide |
| | Iloprost |
| | Indapamide |
| | Irbesartan |
| | Ivabradine |
| | Labetalol |
| | Lacidipine |
| | Lercanidipine |
| | Lisinopril |
| | Losartan |
| | Olmesartan |
| | Perindopril |
| | Prazosin |
| | Quinapril |
| | Ramipril |
| | Ranolazine |
| ☐ | Riociguat (j) |
| | Sacubitril |
| | Sildenafil |
| | Spironolactone |
| | Tadalafil |
| | Telmisartan |
| | Terazosin |
| | Torasemide |
| | Trandolapril |
| | Valsartan |
| **Immunosuppressants** | |
| | Adalimumab |
| | Azathioprine |
| | Basiliximab |
| | Belatacept |
| | Ciclosporin (k) |
| | Etanercept |
| | Everolimus |
| | Leflunomide |
| | Methotrexate |
| | Mycophenolate |
| | Sirolimus |
| | Tacrolimus (l) |
| | Voclosporin |
| **Lipid lowering agents** | |
| ☐ | Atorvastatin |
| | Clofibrate |
| | Evolocumab |
| | Ezetimibe |
| | Fenofibrate |
| | Fluvastatin |
| | Gemfibrozil |
| | Lovastatin |
| | Pitavastatin |
| | Pravastatin |
| ☐ | Rosuvastatin |
| | Simvastatin |

| Multiple sclerosis agents | |
|---|---|
| | Alemtuzumab |
| | Baclofen |
| ☐ | Cladribine |
| | Dantrolene sodium |
| | Dimethyl fumarate |
| | Fampridine |
| | Fingolimod |
| | Glatiramer acetate |
| | Natalizumab |
| | Ocrelizumab |
| | Ozanimod |
| | Peginterferon beta-1a |
| | Siponimod |
| | Teriflunomide |
| **Others** | |
| | Alendronic acid |
| | Alfuzosin |
| | Allopurinol |
| | Calcium supplement |
| | Colchicine |
| | Donepezil |
| | Ergometrine (ergonovine) |
| | Ergotamine |
| | Finasteride |
| | Hydroxychloroquine |
| | Infliximab |
| | Levodopa |
| | Levothyroxine |
| | Memantine |
| | Methotrexate |
| | Mirabegron (m) |
| | Modafinil |
| | Pramipexole |
| | Pyridostigmine |
| ☐ | Rifabutin (n) |
| ✖ | Rifampicin |
| ✖ | Rifapentine |
| ☐ | Tamsulosin (o) |
| **Steroids** | |
| | Beclomethasone |
| | Betamethasone |
| | Ciclesonide |
| | Clobetasol |
| | Fludrocortisone |
| | Flunisolide |
| | Fluticasone |
| | Hydrocortisone |
| | Methylprednisolone |
| | Mometasone |
| | Prednisolone |
| | Prednisone |
| ☐ | 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**<br>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**<br>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**<br>Risk of serious toxicity. Only start NMV/r if the drug can be safely paused or replaced.<br>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**<br>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**<br>Ideally, only start NMV/r if the drug can be safely paused or replaced.<br>Alternatively, dose adjust/monitor. Refer to www.covid19-druginteractions.org for detailed information. |
| | **Potential interaction**<br>Manageable by counselling patient | **Proceed with NMV/r**<br>Interaction manageable by counselling the patient about potential interaction and advising to temporarily stop the drug if feeling unwell. |
| | **Weak interaction**<br>No action needed | **Proceed with NMV/r**<br>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) Ritonavir reduces the conversion to clopidogrel's active metabolite leading to insufficient inhibition of platelet aggregation. Thus, it is recommended to avoid NMV/r in patients at very high-risk of thrombosis (e.g. early period post coronary stenting) unless clopidogrel can be switched to the non-interacting drug prasugrel. However, NMV/r treatment is possible in other clinical situations for which a transient loss in clopidogrel efficacy is acceptable (e.g. alternative to aspirin in intolerant patients).

b) 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.

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

d) Monitor INR as clinically indicated.

e) Decision to hold or dose adjust the cancer drug should be made in conjunction with the patient's oncologist. Consult www.covid19-druginteractions.org for details related to dosage adjustment.

f) Accelerated or blast phase chronic myelogenous leukaemia: do not co-administer, use alternative COVID-19 therapy. In the indication of chronic phase chronic myelogenous leukaemia, the decision to hold or dose adjust the cancer drug should be made in conjunction with the patient's oncologist. If it is decided to hold treatment, restart the cancer drug at least 3 days after completing NMV/r. Alternatively dose adjust, consult www.covid19-druginteractions.org for details.

g) The decision to hold ibrutinib treatment should be made in conjunction with the patient's oncologist. It may be dangerous to interrupt therapy in patients with high volume chronic lymphocytic leukaemia or mantle cell lymphoma due to disease flare and/or cytokine release. Consider an alternative COVID-19 therapy.

h) Strong CYP3A4 inhibitors can substantially increase midostaurin exposure. Consider an alternative COVID-19 treatment.

i) Coadministration with NMV/r is contraindicated at initiation and during the dose-titration phase to minimize the risk of tumour lysis syndrome. Use an alternative COVID19 therapy.

j) The European product label for riociguat does not recommend its use in presence of strong inhibitors; the US product label recommends to start riociguat at a dose of 0.5 mg three times daily and to monitor for signs and symptoms of hypotension.

k) The management of this interaction is challenging and would require dosage adjustment and therapeutic drug monitoring (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) during treatment with NMV/r (days 1-5). Ciclosporin concentrations should be assessed on day 6 or 7 and repeated every 2-4 days.

l) The management of this interaction is challenging and would require a substantial reduction in tacrolimus dosage. Considering the complex management of this interaction, an alternative COVID treatment will need to be considered. However, if TDM for tacrolimus is available, it has been suggested to withhold all tacrolimus doses during treatment with NMV/r (days 1-5). It is advised to measure tacrolimus concentrations on day 3 to assess the need for a one-time tacrolimus dose during NMV/r treatment. Tacrolimus concentrations should be assessed on day 6 or 7 (and every 2-4 days thereafter) and concentrations used to guide the continued withholding or gradual reintroduction of tacrolimus.

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

n) Rifabutin is dosed at 150 mg once daily with NMV/r.

o) Pause tamsulosin and restart 3 days after completing nirmatrelvir/ritonavir. Alternatively, consider using tamsulosin 0.4 mg/day or every other day with monitoring for hypotension. The dose of tamsulosin should not exceed 0.4 mg/day if coadministered.