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

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

Interaction tables - refer to pages 3 and 4 for legend, abbreviations and notes

Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister.
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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 (l)
Leflunomide
Methotrexate
Mycophenolate
Sirolimus (m)
Tacrolimus (n)
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 (o)
Modafinil
Pramipexole
Pyridostigmine
☐ Rifabutin (p)
✖ Rifampicin
✖ Rifapentine
☐ Tamsulosin (q)
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** 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) 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 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.

l) 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.

m) A large increase in sirolimus exposure is predicted in presence of NMV/r. Avoid use of NMV/r unless close monitoring of sirolimus concentrations is feasible. If coadministered, hold sirolimus and start NMV/r 24-48 hours after the last sirolimus dose. Check, sirolimus concentrations 1-2 days after the last dose of NMV/r. If concentrations are supratherapeutic, continue to hold sirolimus and repeat concentration monitoring in 5-7 days to assess resumption. If concentrations are therapeutic/subtherapeutic, resume sirolimus at 50% of baseline dose. Repeat concentration monitoring every 7 days and dose-adjust accordingly.

n) The management of this interaction is challenging and would require a substantial reduction in tacrolimus dosage. Given the complex management of this interaction, consider an alternative COVID treatment. However, if frequent TDM for tacrolimus is available, hold tacrolimus and start NMV/r 12 hours (immediate tacrolimus release) or 24 hours (extended tacrolimus release) after the last tacrolimus dose. Tacrolimus concentrations should be assessed on day 6 or 7 (and every 2-4 days thereafter) and resumption of tacrolimus should begin once drug concentrations approach the therapeutic target. If concentrations are supratherapeutic, continue to withhold tacrolimus. If concentrations are therapeutic, restart tacrolimus at 25-50% of baseline dose. If concentrations are subtherapeutic, restart tacrolimus at 25-75% of baseline dose. Frequent re-assessment should continue for at least two weeks given the variable time course of CYP3A enzyme recovery.

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

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

q) Pause tamsulosin and restart 3 days after completing NMV/r. 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.