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.
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	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
☐	Tiagabine
	Topiramate
	Valproate
	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
	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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Interactions with Outpatient Medicines & Nirmatrelvir/ritonavir (NMV/r)

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

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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 (IDU)
	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
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
IDU = 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.

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