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

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

Please check [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org) for updates.

Drug interaction data for many agents are limited or absent. 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
- Morphine
- Naproxen
- Oxydode
- Paracetamol
- Pethidine
- Tapentadol
- Tramadol

## 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
- Mapiroline
- Mianserin
- Mirtazapine
- Noradoxetine
- Paroxetine
- Reboxetine
- Sertraline
- St John’s Wort
- Trazodone
- Venlafaxine
- Vortioxetine

## Antidiabetics
- Acarbose
- Canagliflozin
- Dapagliflozin
- Dulaglutide
- Empagliflozin
- Exenatide
- Glibenclamide
- Gliclazide
- Glimiprside
- Glipizide
- Insulin
- Linagliptin
- Liraglutide
- Metformin
- Pioglitazone
- Rosiglitazone
- Saxagliptin
- Sitagliptin
- Tolbutamide
- Vildagliptin

## Antipsychotics
- Aripiprazole
- Asenapine
- Chlorpromazine
- Clozapine
- Fluphenazine
- Haloperidol
- Iloperidone
- Levomepromazine
- Lumateperone
- Lurasidone
- Olanzapine
- Paliperidone
- Pericizace
- Perphenazine
- Pimozide
- Propiotizine
- Quetiapine
- Risperidone
- Sulpiride
- Tiapride
- Ziprasidone

## Beta blockers
- Atenolol
- Bisoprolol
- Carvedilol
- Metoprolol
- Nebivolol
- Propranolol
- Sotalol
- Timolol

## Bronchodilators
- Albuterol
- Fluticasone
- Formoterol
- Ipratropium bromide
- Montelukast
- Olodaterol
- Rotflumilast
- Salbutamol
- Salmeterol
- Theophylline
- Umeclidinium bromide
- Vilanterol

## Antihistamines
- Cetirizine
- Fexofenadine
- Loratadine

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- Atenolol
- Bisoprolol
- Carvedilol
- Metoprolol
- Nebivolol
- Propranolol
- Sotalol
- Timolol

## Benzodiazepines
- Alprazolam
- Bromazepam
- Buspirone
- Clonazepam
- Diazepam
- Estazolam
- Flunitrazepam
- Flurazepam
- Lorazepam
- Lormetazepam
- Midazolam
- Oxazepam
- Temazepam
- Triazolam
- Zaleplon
- Zolpidem
- Zopiclone

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- Quetiapine
- Risperidone
- Sulpiride
- Tiapride
- Ziprasidone

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


due to ongoing updates, we recommend checking www.covid19-druginteractions.org regularly.

**Calcium channel blockers**
- Amlodipine
- Diltiazem
- Felodipine
- Nicardipine
- Nifedipine
- Nitrendipine
- Verapamil

**Cancer drugs**
- Abacavir (e)
- Abiraterone
- Acalabrutinib
- Aflatinib
- Alemtuzumab
- Atezolizumab
- Bosutinib
- Capcitabine
- Certitinib (e)
- Dasatinib (f)
- Enocafenib (e)
- Enalaprilat
- Erlotinib (e)
- Fostamatinib
- Gilteritinib (e)
- Ibrutinib (e)
- Imatinib
- Ivosidenib
- Lenalidomide
- Midostaurin (h)
- Neratinib
- Nilotinib (f)
- Olaparib (e)
- Osimertinib
- Palbociclib (e)
- Pazopanib (e)
- Pomalidomide
- Ribociclib (e)
- Sotorasib
- Sunstitinib (e)
- Tamoxifen
- Venetoclax (l)
- Vinblastine (e)
- Vincristine (e)

**Contraceptives**
- Desogestrel (COC)
- Desogestrel (POP)
- Ethinylestradiol
- Etonogestrel (IMP)
- Etonogestrel (VR)
- Levonorogestrel (COC)
- Levonorogestrel (IUD)
- Levonorogestrel (POP)
- Medroxyprogesterone (depot injection)
- Norethisterone (COC)
- Norethisterone (IM)
- Norethisterone (POP)
- Norgestrel (COC)

**Cystic fibrosis agents**
- Ivcacitor
- Ivacaftor/ lumacaftor
- Ivacaftor/tezacaftor
- Ivacaftor/tezacaftor/eleaxacator

**Gastrointestinal agents**
- Antacids
- Citric acid
- Aprepitant
- Domperidone
- Esomeprazole
- Famotidine
- Lansoprazole
- Loperamide
- Mesalamine
- Metoclopramide
- Omeprazole
- Ondansetron
- Pantoprazole
- Rabeprazole
- Ranitidine

**HCV antivirals**
- Ledipasvir/sofosbuvir
- Sofosbuvir/velpatasvir

**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
- Amlodipine
- Bosentan
- Candesartan
- Captopril
- Cilazapril
- Eperenerone
- Sposartan
- Fosinopril
- Furosemide
- Hydrochlorothiazide
- Hydroxychloroquine
- Iloprost
- Indapamide
- Irbesartan
- Ivabradine
- Ledetalol
- Lercanidipine
- Lisinopril
- Losartan
- Olmesartan
- Perindopril
- Prazosin
- Quinapril
- Ramipril
- Ranolazine
- Riociguat (i)

**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
- Alifozin
- Allopurinol
- Calcium supplement
- Colchicine
- Donepezil
- Ergometrine (ergonovine)
- Ergotamine
- Finasteride
- Hydroxychloroquine
- Infliximab
- Levodopa
- Levotiroxine
- Memantine
- Methotrexate
- Mirabegron (q)
- Modafinil
- Pimipexole
- Pyridostigmine
- Rifabutin (p)
- Rifampin
- Rifapentine
- Tamulosin (q)

**Steroids**
- Beclometasone
- Betamethasone
- Ciclesonide
- Clofazimine
- Dexamethasone
- Fludrocortisone
- Flunisolide
- Fluticasone
- Hydrocortisone
- Methylprednisolone
- Mometasone
- Prednisolone
- Prednisone
- Triamcinolone
Legend

<table>
<thead>
<tr>
<th>Colour/Symbol</th>
<th>Recommendation for NMV/r use</th>
</tr>
</thead>
<tbody>
<tr>
<td>![ ]</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>![ ]</td>
<td>Do not use NMV/r ( \rightarrow ) alternative COVID-19 therapy</td>
</tr>
<tr>
<td>![ ]</td>
<td>Risk of serious toxicity. Stopping the drug does not mitigate the interaction due to its prolonged half-life.</td>
</tr>
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</tr>
<tr>
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<td>Strong inducer can jeopardize NMV/r efficacy due to persisting induction after stopping the drug.</td>
</tr>
<tr>
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<td>Do not co-administer</td>
</tr>
<tr>
<td>![ ]</td>
<td>NMV/r use ONLY possible if drug is paused or replaced by a non-interacting drug</td>
</tr>
<tr>
<td>![ ]</td>
<td>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.</td>
</tr>
</tbody>
</table>

- 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
- IM = intramuscular
- IMP = implant
- IM = intrauterine device
- 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-titratiion 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 reduced dosing or use with caution. 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.

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 ciclosporin dose. 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 supertherapeutic, 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 supertherapeutic, 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.