Nirmatrelvir and ritonavir

FOR THE TREATMENT OF COVID-19

Information for health professionals

Funded by the European Union

PAHO Pan American Health Organization World Health Organization

Food and Agriculture Organization of the United Nations

World Organisation for Animal Health Founded as OIE

In partnership with Canada

Contents

2	Description	5	Special warnings and precautions	8	Antiviral activity
2	Mechanism of action	6	Dosage	8	Preclinical toxicity
3	Indications	7	Dose adjustment	8	Pharmacovigilance
3	Limitations of use	7	Presentation	9	References
4	Duration of treatment	7	Drug interactions	10	Annex 1. Drugs highly dependent on CYP3A
4	Adverse reactions	8	Storage	11	Annex 2. Drugs that are potent CYP3A inducers
4	Contraindications	8	Clinical efficacy	12	Annex 3. Main established drug interactions and other potentially significant drug interactions

Description

This treatment is based on nirmatrelvir and ritonavir. These two oral antiviral medicines are supplied for use at home as a single pack (trade name, Paxlovid™). Several international regulatory authorities (see references) have granted it emergency use authorization for the treatment of non-severe non-critical COVID-19 in patients at high risk of hospitalization (*1*–*6*).

The combination of nirmatrelvir with ritonavir is a superior treatment option because it may be more effective in preventing hospitalization for COVID-19 and it has a better risk profile than molnupiravir. It is also easier to administer than intravenous remdesivir or antibodies (*1*).

Health professionals should be aware of the potential benefits and risks of using the nirmatrelvir/ritonavir combination, **particularly with regard to potential drug interactions,** and are encouraged to notify national pharmacovigilance systems regarding any suspected adverse reaction to these medicines.

The nirmatrelvir/ritonavir combination should not be used as a substitute for COVID-19 vaccination or for the prevention of SARS-CoV-2 infection.

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), rendering it incapable of processing polyprotein precursors which prevents viral replication (*4*).

Ritonavir acts as a pharmacokinetic enhancer. It inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir (*4, 5*).

Indications

The combination of nirmatrelvir with ritonavir is indicated for the treatment of mild to moderate COVID-19 in persons with a positive COVID-19 test and who are at high risk for progression to severe or critical disease and hospitalization (*1–6*).

In the absence of evidence on its efficacy and safety, nirmatrelvir with ritonavir is not recommended for use in children under 18 years or in pregnant or breast-feeding women with COVID-19. Nor is it recommended in patients taking any medicines with which nirmatrelvir or ritonavir may have potentially dangerous drug interactions (*1*).

The nirmatrelvir-ritonavir combination should not be used in patients at low risk of hospitalization for COVID-19 as the benefits were found to be negligible (*1*).

Treatment with nirmatrelvir and ritonavir should be initiated as soon as possible after a COVID-19 diagnosis, ideally within 5 days of symptom onset (*1–3*).

Combining various antiviral therapies is not recommended because there is no evidence regarding their use (*1*).

People at **increased risk of hospitalization or death from COVID-19 include** (*7*):

- Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection, regardless of vaccination status.
- Unvaccinated individuals aged 75 years or over, or aged 65 years or over with additional risk factors (presence of two or more comorbidities: hypertension, obesity [body mass index >30], diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, cerebrovascular disease, thrombocytopenia, active smoking, and cancer).

Before prescribing nirmatrelvir with ritonavir, health personnel should carefully review all concomitant medicines the patient is taking, including over-the-counter products and herbal supplements, to assess possible drug interactions (see "Contraindications" and "Drug interactions" and Annexes for further information).

Limitations of use

Nirmatrelvir with ritonavir should not be used in (*3*):

- **patients with severe or critical COVID-19 infection.**
- **patients with symptoms for more than 5 days.**
- **for longer than 5 consecutive days.**

Duration of treatment

The duration of treatment with nirmatrelvir and ritonavir is 5 consecutive days (*1*). Patients should be instructed not to interrupt the course of treatment and continue until it is completed, even if the patient requires hospitalization for severe or critical COVID-19 after starting treatment (*5*).

Adverse reactions

The most common adverse reactions reported during treatment with ritonavir and nirmatrelvir were dysgeusia (5.6%), diarrhea (3.1%), headache (1.4%), and vomiting (1.1%) (*5*).

Patients should be informed that they must consult their doctor immediately if they present any of the following signs and symptoms of liver disease: loss of appetite, jaundice of skin and mucous membranes, choluria, acholia, pruritus, and abdominal pain (*3*).

Contraindications

- Nirmatrelvir with ritonavir is contraindicated in patients with (*1–5, 8*):
    - A history of clinically significant hypersensitivity reactions (such as toxic epidermal necrolysis or Stevens-Johnson syndrome) to nirmatrelvir, ritonavir, or any other ingredients in the formulation.
    - Severe hepatic impairment.
    - Severe renal impairment.
- Co-administration of the nirmatrelvir/ritonavir combination with the following drug classes is contraindicated (*1–5*):
    - Drugs highly dependent on the CYP3A enzyme for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. Some examples of this type of drug are listed in **Table A1**.
    - Potent CYP3A inducers as reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. Examples of these drugs are listed in **Table A2**.
    - Treatment with nirmatrelvir and ritonavir must not be started immediately after discontinuation of any CYP3A-inducing medicines due to the delayed offset of the recently discontinued CYP3A inducer (*5*).

Special warnings and precautions

Pediatric patients

- The safety and efficacy of nirmatrelvir with ritonavir in children under 18 years of age have not been established (*1, 2, 4, 5*).

The emergency use authorization of nirmatrelvir/ritonavir in the United States indicates its use for the treatment of pediatric patients aged 12 years and older weighing at least 40 kg with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death (*3*).

Pregnancy

- No information is available on the safety of nirmatrelvir with ritonavir during pregnancy, so use is not recommended (*1–5*). If use is necessary, the benefits and risks of treatment with nirmatrelvir and ritonavir during pregnancy should be weighed (*3*).

Lactation

- There are no available data on the safety of nirmatrelvir with ritonavir during lactation, so breast-feeding is not recommended during treatment and for up to 7 days after the last dose (*1–5*).

Limited published data report that ritonavir is present in breast milk. There is no information on the effects, so possible risks to the infant cannot be excluded (*4*).

People with a female reproductive system

- No information is available on the risk of conceiving when taking nirmatrelvir/ritonavir. People with a female reproductive system should either abstain from sex or should use reliable contraception during treatment and for 7 days after the last dose (*1–5*).

Ritonavir may reduce the effectiveness of combined hormonal contraceptives. People using hormonal contraception should be advised to use an effective alternative method of contraception or add a barrier method during treatment with nirmatrelvir/ritonavir and until one full menstrual cycle after stopping treatment (*2–5, 8*).

Effects on laboratory tests

- **Ritonavir has been associated with alterations in cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), creatine phosphokinase (CPK), and uric acid concentrations (*4*).**

Risk of serious adverse reactions from interaction with other medicines

- **Co-administration of nirmatrelvir and ritonavir with other medicines may result in potentially significant drug interactions and produce life-threatening serious adverse reactions (*2–5*).**
- **Serious consideration needs to be given to potential drug interactions in any patient being considered for nirmatrelvir/ritonavir treatment.**

  Table A3 lists the main interactions associated with nirmatrelvir/ritonavir therapy. It is also recommended to consult the Liverpool COVID-19 Interaction Checker (*9*).

Hepatotoxicity

- **Elevated liver transaminases, clinical hepatitis, and jaundice have been observed in patients taking ritonavir; therefore, caution should be exercised when administering the nirmatrelvir/ritonavir combination to patients with pre-existing liver disease, liver enzyme abnormalities, or hepatitis (*3–5*).**

Human immunodeficiency virus type 1 (HIV-1) drug resistance

- **Because nirmatrelvir is co-administered with low-dose ritonavir, there is a risk of developing resistance to HIV protease inhibitors in people with uncontrolled or undiagnosed HIV-1 infection (*3–5*).**

Allergic and hypersensitivity reactions

- **Allergic-type reactions have been reported with the use of the nirmatrelvir/ritonavir combination. If a clinically significant hypersensitivity reaction or anaphylaxis occurs, treatment should be immediately discontinued and appropriate medications and supportive care initiated.**

Dosage

- The recommended dose is 300 mg of nirmatrelvir (two 150 mg tablets) with 100 mg of ritonavir (one 100 mg tablet) taken together orally every 12 hours, with or without food, for 5 days. The tablets should be swallowed whole and not chewed, broken, or crushed (*1–5*).

- The nirmatrelvir and ritonavir doses should be taken simultaneously to ensure sufficient nirmatrelvir plasma levels to achieve the desired antiviral effect (*4*).
- In the case of a **missed dose**, if less than 8 hours have passed since the time it is usually taken, the patient should take the missed dose as soon as possible and then take the next dose at the usual time. If more than 8 hours have passed, the patient should not take the missed dose but wait and take the next scheduled dose. The patient should not take a double dose to make up for a missed dose (*5*).

Dose adjustment

- **Renal impairment** (*2–5*)
  - **Mild (estimated glomerular filtration rate (eGFR): ≥60 to <90 ml/min).** No nirmatrelvir/ritonavir dose adjustment necessary.
  - **Moderate (eGFR ≥30 to <60 ml/min).** To prevent increased toxicity, the dose should be reduced to 150 mg nirmatrelvir and 100 mg ritonavir, taken together orally every 12 hours for 5 days.
  - **Severe (eGFR <30 ml/min).** Use is contraindicated until more data on the appropriate dose are available.
- **Liver damage**
  - **Mild to moderate.** No nirmatrelvir/ritonavir dose adjustment necessary.
  - **Severe.** No pharmacokinetic or safety data are available regarding its use in people with severe hepatic impairment, therefore treatment is contraindicated.
  - **Elderly patients.** No dose adjustment recommended.
  - **HIV-1 patients:** No dose adjustment of HIV-1 drugs is required with the exception of maraviroc. Follow-up by a physician is important to monitor for possible side effects (*8*).

Presentation

The nirmatrelvir/ritonavir combination consists of two medicines packaged together: nirmatrelvir 150 mg coated tablets and ritonavir 100 mg coated tablets.

Drug interactions

There are many potentially significant drug interactions to be considered when using nirmatrelvir/ritonavir, mainly due to the ritonavir component. Co-administration with other medicines must be carefully reviewed. **Table A3** lists the main interactions and the precautions to be followed. Use of the University of Liverpool COVID-19 Drug Interaction Checker is also recommended (available from: https://www.covid19-druginteractions.org/checker).

- Patients taking ritonavir- or cobicistat-containing HIV or hepatitis C virus (HCV) regimens should continue their treatment as indicated (*3, 4*).

Storage

Store nirmatrelvir and ritonavir in the original packaging from 20 °C to 25 °C (68 °F to 77 °F) away from moisture, heat, or sunlight. Do not refrigerate or freeze (*3–5*). Storage temperature excursions permitted between 15 °C and 30 °C (59 °F to 86 °C) (*3*).

Clinical efficacy

The efficacy of nirmatrelvir/ritonavir was determined in the interim and final analysis of the EPIC-HR phase 2/3, randomized, double-blind, placebo-controlled clinical trial in 3078 non-hospitalized symptomatic adults with a laboratory-confirmed diagnosis of SARS-CoV-2 infection and risk of progressing to severe or critical disease (*5*).

The findings of this study revealed that in groups at high risk (over 10% risk) of hospitalization, treatment with nirmatrelvir plus ritonavir reduces the risk by 85%, which means 84 fewer hospitalizations per 1000 patients (*1*).

Antiviral activity

Nirmatrelvir exhibited antiviral activity in in vitro assays with differentiated NHBE cells (a human lung alveolar epithelial cell line), after 3 days of exposure, against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529) variants. The Beta (B.1.351) variant was the least susceptible tested variant (*5*).

Preclinical toxicity

No non-clinical safety and toxicity studies have been conducted with the combination. The available data correspond to the non-clinical evaluation of each active substance individually (*4, 5*).

Pharmacovigilance

Nirmatrelvir with ritonavir is a provisionally authorized medicinal product which does not have relevant post-authorization data. Its use should be accompanied by active pharmacovigilance (*1*).

Healthcare professionals should document all suspected adverse reactions in treated patients and report them to the national pharmacovigilance system (*1, 7*).

References

1. World Health Organization. WHO Living guideline: Drugs to prevent COVID-19. 2022. Geneva: WHO; 2021 [cited 27 September 2022]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.5.

2. Medicines and Healthcare Products Regulatory Agency; Package leaflet: Information for the patient. Paxlovid 150 mg/100 mg film-coated tablets. PF-07321332/ritonavir. London: MHRA; 2022 [cited 27 September 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045768/Reg_PIL_PX_2_0_GB.pdf.

3. United States Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. Silver Spring: FDA; 2022 [cited 27 September 2022]. Available from: https://www.fda.gov/media/155050/download.

4. Therapeutic Goods Administration. Australian Product Information –Paxlovid^{tm} (nirmatrelvir-ritonavir tablets). Canberra: TGA; 2022 [cited 27 September 2022]. Available from: https://www.tga.gov.au/sites/default/files/paxlovid-pi.pdf.

5. European Medicines Agency. EPAR Paxlovid. Annex I. Summary of Product Characteristics. Amsterdam: EMA; 2022 [cited 27 September 2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf.

6. Therapeutic Goods Administration. Drug guideline. Use of nirmatrelvir and ritonavir tablets for COVID-19. Canberra: TGA; 2022 [cited 27 September 2022]. Available from: https://www.cec.health.nsw.gov.au/__data/assets/pdf_file/0007/702817/Drug-guideline-use-of-nirmatrelvir-and-ritonavir-tablets-for-COVID-19.PDF.

7. Pan American Health Organization. Considerations on the use of antivirals, monoclonal antibodies, and other interventions for the management of COVID-19 patients in Latin America and the Caribbean. Washington, DC: PAHO; 2022 [cited 27 September 2022]. Available from: https://iris.paho.org/handle/10665.2/55968.

8. United States Food and Drug Administration. PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers. Silver Spring: FDA; 2022 [cited 27 September 2022]. Available from: https://www.fda.gov/media/158165/download.

9. University of Liverpool, the Drug Interaction Group (UK). COVID-19 Drug Interactions. Liverpool: University of Liverpool; 2022 [cited 27 September 2022]. Available from: https://www.covid19-druginteractions.org/checker.

Annex 1. Drugs highly dependent on CYP3A

It is contraindicated to co-administer nirmatrelvir/ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious or life-threatening reactions.

Table A1 lists the main medicines that are highly dependent on CYP3A.[1] If a drug is not listed in the table, it is recommended to use the University of Liverpool COVID-19 Drug Interaction Checker (available from: https://www.covid19-druginteractions.org/checker.

Table A1. Main drugs that are highly dependent on CYP3A for clearance

Class	Medication metabolized by CYP3A/ Effect on concentration	Clinical relevance
Cardiovascular agents	eplerenone ivabradine	Co-administration contraindicated due to potential for serious adverse reactions.
Benign prostatic hyperplasia agents	silodosin	Co-administration contraindicated due to potential for postural hypotension.
Analgesics	pethidine propoxyphene (dextro)	Potential for severe respiratory depression or hematologic abnormalities.
Alpha-1-adrenoreceptor antagonists	alfuzosin tamsulosin	Co-administration contraindicated due to potential for hypotension.
Mineralocorticoid receptor antagonists	finerenone	Risk of serious adverse effects including hyperkalemia, hypotension, and hyponatremia.
Serotonin receptor 1A agonist/serotonin receptor 2A antagonist	flibanserin	Potential serious adverse effects, including hypotension, syncope, and CNS depression.
Opioid antagonists	naloxegol	Risk of opioid withdrawal syndrome.
Vasopressin receptor antagonists	tolvaptan	Risk of dehydration, hypovolemia, and hyperkalemia.
Antianginal agents	ranolazine	Potential serious or life-threatening reactions.
Antiarrhythmics	amiodarone dronedarone flecainide propafenone quinidine	Potential for cardiac arrhythmias
Anti-gout	colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Migraine medications	eletriptan ubrogepant	Potential for serious cardiovascular and cerebrovascular adverse effects.
Antipsychotics	lurasidone pimozide	Potential for serious adverse effects.
Ergot derivatives	dihydroergotamine ergotamine methylergonovine	Potential for acute toxicity characterized by vasospasm and ischemia of extremities and other tissues including the central nervous system.
Immunosuppressants	voclosporin	Potential for serious adverse effects.

1 Medicines and Healthcare Products Regulatory Agency; Package leaflet: Information for the patient. Paxlovid 150 mg/100 mg film-coated tablets. PF-07321332/ritonavir. London: MHRA; 2022 [cited 27 September 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045768/Reg_PIL_PX_2_0_GB.pdf. United States Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. Silver Spring: FDA; 2022 [cited 27 September 2022]. Available from: https://www.fda.gov/media/155050/download. Therapeutic Goods Administration. Australian Product Information –Paxlovid™ (nirmatrelvir/ritonavir tablets). Canberra: TGA; 2022 [cited 27 September 2022]. Available from: https://www.tga.gov.au/sites/default/files/paxlovid-pi.pdf. European Medicines Agency. EPAR Paxlovid. Annex I. Summary of Product Characteristics. Amsterdam: EMA; 2022 [cited 27 September 2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf.

Class	Medication metabolized by CYP3A/ Effect on concentration	Clinical relevance
HMG-CoA reductase inhibitors	lovastatin simvastatin	Potential for myopathy including rhabdomyolysis.
Phosphodiesterase type 5 (PDE5) inhibitors	sildenafil, when used for pulmonary arterial hypertension	Due to the potential for adverse events associated with sildenafil, such as visual abnormalities, hypotension, prolonged erection, and syncope.
Microsomal triglyceride transfer protein (MTP) inhibitors	lomitapide	Potential for hepatotoxicity and gastrointestinal adverse reactions.
Hypnotics/sedatives	triazolam midazolam (oral)	Potential for extreme sedation and respiratory depression.

Annex 2. Drugs that are potent CYP3A inducers

Co-administration of the nirmatrelvir and ritonavir combination with potent CYP3A inducers is contraindicated because reduced nirmatrelvir or ritonavir plasma concentrations may be associated with loss of virologic response and resistance to these drugs. Treatment with nirmatrelvir and ritonavir cannot be started immediately after discontinuation of a CYP3A inducer.

Table A2 lists the main drugs that are potent CYP3A inducers.[1] If a drug is not listed in the table, it is recommended to use the University of Liverpool COVID-19 Drug Interaction Checker (available from: https://www.covid19-druginteractions.org/checker).

Table A2. Main drugs that are potent CYP3A inducers

Class	Potent enzyme-inducer	Effect on nirmatrelvir-ritonavir concentration	Clinical relevance
Anticancer agents	apalutamide	Decrease	May be associated with loss of virologic response and resistance.
Anticonvulsants	carbamazepine phenobarbital phenytoin primidone		
Antimycobacterials	rifampicin		
Herbal products	St. John's wort (*Hypericum perforatum*)		
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor		

1 Medicines and Healthcare Products Regulatory Agency; Package leaflet: Information for the patient. Paxlovid 150 mg/100 mg film-coated tablets. PF-07321332/ritonavir. London: MHRA; 2022 [cited 27 September 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045768/Reg_PIL_PX_2_0_GB.pdf. United States Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. Silver Spring: FDA; 2022 [cited 27 September 2022]. Available from: https://www.fda.gov/media/155050/download. Therapeutic Goods Administration. Australian Product Information –Paxlovid™ (nirmatrelvir/ritonavir tablets). Canberra: TGA; 2022 [cited 27 September 2022]. Available from: https://www.tga.gov.au/sites/default/files/paxlovid-pi.pdf. European Medicines Agency. EPAR Paxlovid. Annex I. Summary of Product Characteristics. Amsterdam: EMA; 2022 [cited 27 September 2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf.

Annex 3. Main established drug interactions and other potentially significant drug interactions

Table A3 lists clinically significant drug interactions, including contraindicated drugs[1]. The list is a guide and not considered a comprehensive list of all possible drugs that may interact with nirmatrelvir and ritonavir. If a drug is not listed in the table, it is recommended to use the University of Liverpool COVID-19 Drug Interaction Checker (available from: https://www.covid19-druginteractions.org/checker).

Table A3. Main established drug interactions and other potentially significant drug interactions

Legend	
↑	increased concentration
↓	decreased concentration
↔	remains unchanged
	Co-administration of these drugs with nirmatrelvir and ritonavir is contraindicated.
	Co-administration of these drugs with nirmatrelvir and ritonavir requires precautions as indicated in each case.

Class	Drug	Effect on concentration	Comments
Adrenergic agonists	amphetamines and derivatives	↑ amphetamines and derivatives	Close monitoring of adverse effects is recommended when co-administered.
Beta-3 adrenergic agonist	mirabegron	↑ mirabegron	For concomitant use in patients with renal or hepatic impairment, consult additional prescribing information.
Long-acting beta-adrenergic agonist	salmeterol	↑ salmeterol	Co-administration is contraindicated due to risk of serious adverse cardiovascular effects associated with salmeterol.
Analgesics	pethidine propoxyphene	↑ pethidine ↑ propoxyphene	Co-administration is contraindicated due to risk of serious respiratory depression or hematological abnormalities.
	piroxicam	↓ piroxicam	Piroxicam levels may decrease due to ritonavir.

1 United States Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. Silver Spring: FDA; 2022 [cited 27 September 2022]. Available from: https://www.fda.gov/media/155050/download. Therapeutic Goods Administration. Australian Product Information –Paxlovidtm (nirmatrelvir/ritonavir tablets). Canberra: TGA; 2022 [cited 27 September 2022]. Available from: https://www.tga.gov.au/sites/default/files/paxlovid-pi.pdf. European Medicines Agency. EPAR Paxlovid. Annex I. Summary of Product Characteristics. Amsterdam: EMA; 2022 [cited 27 September 2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf. University of Liverpool, the Drug Interaction Group (UK). COVID-19 Drug interactions. Liverpool: University of Liverpool; 2022 [cited 27 September 2022]. Available from: https://www.covid19-druginteractions.org/checker.

Class	Drug	Effect on concentration	Comments
Narcotic analgesics	buprenorphine norbuprenorphine fentanyl methadone morphine oxycodone hydrocodone	↑ buprenorphine ↑ norbuprenorphine ↑ fentanyl ↑ oxycodone ↑ hydrocodone ↓ methadone ↓ morphine	Close monitoring for adverse effects (including life-threatening respiratory depression) is recommended with co-administration. Close monitoring for withdrawal effects is required when co-administered with methadone. Adjust the methadone dose if necessary. Morphine levels may be decreased due to induction of glucuronidation by ritonavir.
Anxiolytics	clorazepate (nordiazepam) diazepam estazolam flurazepam midazolam triazolam	↑ clorazepate (nordiazepam) ↑ diazepam ↑ estazolam ↑ flurazepam ↑ midazolam ↑ triazolam	Co-administration is contraindicated due to potential for serious adverse effects.
	alprazolam buspirone clobazam flunitrazepam zopiclone	↑ alprazolam ↑ buspirone ↑ clobazam ↑ flunitrazepam ↑ zopiclone	When administered concomitantly, it is recommended to monitor closely for adverse effects and, if necessary, adjust the dose.
Alpha-1 adrenergic receptor antagonists	alfuzosin tamsulosin	↑ alfuzosin ↑ tamsulosin	Co-administration is contraindicated due to possible hypotension. Alfuzosin or tamsulosin therapy should be restarted 3 days after taking the last nirmatrelvir-ritonavir dose.
Endothelin receptor antagonists	bosentan	↑ bosentan	Bosentan should be discontinued at least 36 hours before starting nirmatrelvir-ritonavir.
Anti-asthmatic agents	theophylline	↓ theophylline	An increased theophylline dose may be necessary due to the effect of ritonavir.
Antianginal agents	ranolazine	↑ ranolazine	Co-administration is contraindicated due to potential serious or life-threatening adverse effects.
Antiarrhythmics	amiodarone bepridil dronedarone encainide flecainide propafenone quinidine	↑ antiarrhythmics	Co-administration is contraindicated due to risk of cardiac arrhythmias.
	digoxin lidocaine (systemic)	↑ antiarrhythmics	When administered concomitantly, caution is advised and the therapeutic concentration of the antiarrhythmic should be monitored.

Class	Drug	Effect on concentration	Comments
Anticancer agents	acalabrutinib apalutamide enzalutamide ivosidenib	↓ nirmatrelvir-ritonavir ↑ acalabrutinib ↑ apalutamide ↑ ivosidenib	Co-administration is contraindicated because it may be associated with loss of virologic response and resistance, as well as the potential for serious adverse effects.
	bosutinib ibrutinib midostaurin neratinib venetoclax	↑ bosutinib ↑ ibrutinib ↑ midostaurin ↑ neratinib ↑ venetoclax	Co-administration is contraindicated due to potential serious adverse effects.
	abemaciclib afatinib ceritinib dasatinib encorafenib erlotinib fostamatinib gilteritinib imatinib nilotinib olaparib palbociclib pazopanib ribociclib sunitinib vinblastine vincristine	↑ anticancer agent	Co-administration should be avoided due to possible adverse effects.
Antiplatelet anticoagulants	apixaban rivaroxaban ticagrelor clopidogrel (stent) vorapaxar	↑ apixaban ↑ rivaroxaban ↑ ticagrelor ↓ clopidogrel ↑ vorapaxar	Co-administration is not recommended due to risk of bleeding/thrombosis; the apixaban dose should be adjusted if necessary. Co-administration with rivaroxaban or ticagrelor is not recommended due to risk of bleeding/thrombosis. Co-administration with clopidogrel is contraindicated due to the risk of decreased platelet aggregation inhibition in patients at high risk of thrombosis (e.g., early period post coronary stenting). In patients at low risk of thrombosis, co-administration may be considered with monitoring for adverse effects. Co-administration with vorapaxar is contraindicated.
	dabigatran edoxaban phenprocoumon warfarin	↑ dabigatran ↑ edoxaban ↑↓ phenprocoumon ↑↓ warfarin	Dose adjustment is required when used concomitantly. Additional prescribing information should be consulted. If co-administration with warfarin is necessary, the INR[a] should be closely monitored.

Class	Drug	Effect on concentration	Comments
Anticonvulsants	carbamazepine clonazepam phenobarbital phenytoin primidone	↓ nirmatrelvir-ritonavir ↑ carbamazepine ↑ clonazepam ↓ phenobarbital ↓ phenytoin	Co-administration is contraindicated because it may be associated with the potential for loss of virologic response and resistance. Co-administration is contraindicated due to the potential for serious adverse effects.
	ethosuximide tiagabine	↑ ethosuximide ↑ tiagabine	When administered concomitantly, caution and close monitoring of adverse effects are recommended.
Antidepressants	St. John's wort (*Hypericum perforatum*)	↓ nirmatrelvir-ritonavir	Co-administration is contraindicated as it may be associated with loss of virologic response and resistance to nirmatrelvir and ritonavir.
	bupropion (for smoking cessation) desipramine fluoxetine imipramine nortriptyline paroxetine reboxetine trazodone	↓ bupropion and active metabolite hydroxybupropion ↑ desipramine ↑ fluoxetine ↑ imipramine ↑ nortriptyline ↑ paroxetine ↑ reboxetine ↑ trazodone	When administered concomitantly, the clinical response to bupropion and the active metabolite hydroxybupropion should be monitored. May increase the concentration of desipramine, fluoxetine, imipramine, nortriptyline, paroxetine, and reboxetine. Adverse reactions such as nausea, dizziness, hypotension, and syncope have been observed with the co-administration of trazodone and ritonavir. A lower trazodone dose should be considered.
Antidiabetic agents	glibenclamide saxagliptin	↑ glibenclamide ↑ saxagliptin	When administered concomitantly, blood glucose monitoring is recommended with dose adjustments as needed.
Antifungals	voriconazole ketoconazole isavuconazonium sulfate itraconazole	↓ voriconazole ↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir-ritonavir	Co-administration with voriconazole should be avoided. When co-administered with ketoconazole, isavuconazonium sulfate, and itraconazole, additional prescribing information should be consulted.
Anti-gout	colchicine	↑ colchicine	Co-administration is contraindicated due to the potential for serious or fatal adverse effects in patients with renal or hepatic impairment.

Class	Drug	Effect on concentration	Comments
Antihistamines	astemizole terfenadine fexofenadine loratadine	↑ astemizole ↑ terfenadine ↑ fexofenadine ↑ loratadine	Concomitant use with astemizole or terfenadine may increase the risk of serious arrhythmias. Concomitant use increases fexofenadine concentrations. When co-administered with loratadine, monitoring for both therapeutic and adverse effects is recommended.
	aliskiren bosentan eplerenone ivabradine lercanidipine ranolazine	↑ aliskiren ↑ bosentan ↑ eplerenone ↑ ivabradine ↑ lercanidipine ↑ ranolazine	Co-administration is contraindicated due to the potential for serious adverse reactions.
Antihypertensives - heart failure	doxazosin indapamide labetalol lacidipine riociguat sacubitril terazosin valsartan	↑ doxazosin ↑ indapamide ↓ labetalol ↑ lacidipine ↑ riociguat ↑ sacubitril ↑ terazosin ↑ valsartan	When administered concomitantly, caution should be exercised, and patients should be instructed to monitor their blood pressure.
	amlodipine diltiazem felodipine nicardipine nifedipine nitrendipine verapamil	↑ calcium channel blockers	When administered concomitantly, caution should be exercised, and clinical monitoring is recommended; the dose of these medicines may need to be decreased.
Anti-infectives	clarithromycin erythromycin	↑ clarithromycin ↑ erythromycin	When administered concomitantly, additional prescribing information should be consulted to confirm if the dose of the anti-infective needs to be adjusted.
Antimycobacterials	rifampicin rifapentine	↓ nirmatrelvir-ritonavir	Co-administration is contraindicated as it may be associated with loss of virologic response and resistance to nirmatrelvir and ritonavir. Alternative antimycobacterial medicines, such as rifabutin, should be considered.
	bedaquiline delamanid rifabutin	↑ bedaquiline ↑ delamanid ↑ rifabutin	Additional prescribing information is recommended when co-administering with bedaquiline. If co-administration with delamanid is necessary, heart rhythm should be monitored (ECG). For concomitant use, additional prescribing information should be consulted to confirm if it is necessary to reduce the rifabutin dose.
Antimicrobials	↑ fusidic acid (oral/ intravenous)	↑ fusidic acid (oral/ intravenous)	Co-administration of fusidic acid and ritonavir is contraindicated due to the potential for serious side effects.
Migraine medications	eletriptan ubrogepant	↑ eletriptan ↑ ubrogepant	Co-administration with eletriptan is contraindicated due to the potential for serious cardiovascular and cerebrovascular adverse effects. Co-administration with ubrogepant is contraindicated due to the potential for serious side effects. Ubrogepant should be discontinued at least 12 hours before starting treatment with ritonavir and nirmatrelvir

Class	Drug	Effect on concentration	Comments
Antipsychotics	clozapine lumateperone lurasidone pimozide quetiapine	↑ clozapine ↑ lumateperone ↑ lurasidone ↑ pimozide ↑ quetiapine	Co-administration is contraindicated due to the potential for serious adverse reactions. If co-administration is necessary, the quetiapine dose should be reduced and associated adverse reactions should be monitored.
	aripiprazole haloperidol iloperidone risperidone thioridazine ziprasidone	↑ aripiprazole ↑ haloperidol ↑ iloperidone ↑ risperidone ↑ thioridazine ↑ ziprasidone	For co-administration, caution should be exercised, adverse effects carefully monitored, and the dose should be adjusted if necessary.
Anti-HIV	tipranavir atazanavir/ritonavir darunavir/ritonavir	↑ protease inhibitor	With concomitant use, monitor for possible increased adverse effects. Patients taking ritonavir- or cobicistat-containing regimens should continue their treatment as directed.
	efavirenz nevirapine zidovudine bictegravir/ emtricitabine/ tenofovir maraviroc	↑ efavirenz ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir ↑ maraviroc	For concomitant use, the prescribing information of the respective anti-HIV medicines should be consulted. A dose adjustment is required when co-administered with maraviroc. Additional prescribing information should be consulted.[b]
Hepatitis C antivirals	elbasvir/grazoprevir glecaprevir/ pibrentasvir	↑ antiviral	Co-administration is contraindicated; increased grazoprevir concentrations may increase alanine aminotransferase levels.
	ombitasvir/ paritaprevir/ritonavir and dasabuvir sofosbuvir/ velpatasvir/ voxilaprevir	↑ antiviral	Consult additional prescribing information when co-administering. Patients on a hepatitis C virus regimen containing ritonavir should continue treatment as directed and should be monitored for increased adverse effects.
Combined hormonal contraception	ethinyl estradiol	↓ ethinyl estradiol	When used concomitantly with combined hormonal contraceptives, the dose of estrogens, such as ethinyl estradiol, is expected to be reduced. Additional non-hormonal contraception should be used during treatment with ritonavir/nirmatrelvir and until one full menstrual cycle after treatment.
Inhaled, injectable, or intranasal corticosteroids	betamethasone budesonide triamcinolone	↑ corticosteroid	A reduction of the glucocorticoid dose is recommended with close monitoring for local and systemic effects, or switch to an alternative glucocorticoid which is not CYP3A4 substrate (e.g., beclomethasone).
Systemic corticosteroids	dexamethasone	↑ corticosteroid	Concomitant use increases the risk of Cushing's syndrome and adrenal suppression. Alternative corticosteroids should be considered, including beclomethasone and prednisolone.
Ergot derivatives	dihydroergotamine ergometrine (ergonovine) ergotamine methylergonovine	↑ dihydroergotamine ↑ ergometrine (ergonovine) ↑ ergotamine ↑ methylergonovine	Co-administration is contraindicated due to the potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues, including the central nervous system.

Class	Drug	Effect on concentration	Comments
Multiple sclerosis medicines	cladribine	↑ cladribine	Caution should be exercised when co-administered. Administration times should be at least 3 hours apart, with monitoring for possible adverse effects.
Cystic fibrosis medicines	ivacaftor/lumacaftor	↓ nirmatrelvir-ritonavir	Co-administration is contraindicated as it may be associated with loss of virologic response and resistance to nirmatrelvir/ritonavir.
	ivacaftor ivacaftor/tezacaftor ivacaftor/tezacaftor/ elexacaftor	↑ ivacaftor ↑ ivacaftor/tezacaftor ↑ ivacaftor/tezacaftor/ elexacaftor	The dose of these medicines should be decreased when co-administered with nirmatrelvir/ritonavir.
	cisapride domperidone	↑ cisapride ↑ domperidone	Co-administration is contraindicated due to the potential for serious adverse reactions.
Gastro-intestinal medicines	aprepitant loperamide	↑ aprepitant ↑ loperamide	When co-administered, monitor for possible adverse effects. The use of high loperamide doses may cause serious cardiovascular adverse effects.
Cardiac glycosides	digoxin	↑ digoxin	When co-administered, monitor serum digoxin levels.
Hypnotics Sedatives	clorazepate diazepam estazolam flurazepam triazolam, midazolam (oral) pethidine (meperidine) norpethidine (metabolite)	↑ clorazepate ↑ diazepam ↑ estazolam ↑ flurazepam ↑ triazolam ↑ midazolam ↑ pethidine (meperidine) ↑ norpethidine (metabolite)	Co-administration is contraindicated due to the potential for extreme sedation and respiratory depression. Use of pethidine and ritonavir is contraindicated due to the increased concentration of the metabolite, norpethidine, which has analgesic and central nervous system stimulating properties.
	alprazolam buspirone midazolam (parenteral administration)	↑ alprazolam ↑ buspirone ↑ midazolam	An alprazolam dose reduction should be considered, and potential adverse effects should be monitored. Close monitoring of both therapeutic and adverse effects is recommended when co-administering buspirone with ritonavir. Midazolam (parenteral) should be co-administered in a setting that ensures close clinical monitoring and appropriate medical management in the event of respiratory depression or prolonged sedation. A midazolam dose reduction should be considered especially if more than one dose is administered.
Hypnotics (other)	zolpidem	↑ zolpidem	Close monitoring for an excessive increase in the sedative effect is recommended.

Class	Drug	Effect on concentration	Comments
Lipid-lowering agents	lovastatin lomitapide simvastatin	↑ lovastatin ↑ simvastatin ↑ lomitapide	Co-administration with lovastatin or simvastatin is contraindicated due to the potential for myopathy, including rhabdomyolysis. Co-administration with lomitapide is contraindicated due to the potential for hepatotoxicity and gastrointestinal adverse reactions. Lovastatin, lomitapide, and simvastatin should be discontinued at least 12 hours before the first nirmatrelvir-ritonavir dose and not resumed for 5 days after the last nirmatrelvir-ritonavir dose.
	atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with nirmatrelvir/ritonavir. They do not need to be stopped prior to or after completing this treatment.
Phosphodiesterase type 5 (PDE5) inhibitors	For pulmonary hypertension: sildenafil tadalafil	↑ sildenafil ↑ tadalafil	Co-administration is contraindicated due to the potential for serious adverse reactions.
	For erectile dysfunction: avanafil sildenafil tadalafil vardenafil	↑ avanafil ↑ sildenafil ↑ tadalafil ↑ vardenafil	Co-administration may increase the risk of adverse events, such as hypotension, syncope, visual disturbances, and prolonged erection.
Immunosuppressants	cyclosporine everolimus sirolimus tacrolimus voclosporin	↑ cyclosporine ↑ everolimus ↑ sirolimus ↑ tacrolimus ↑ voclosporin	Co-administration is contraindicated due to the potential for serious adverse reactions.
Other	finerenone flibanserin naloxegol silodosin tolvaptan vorapaxar	↑ finerenone ↑ flibanserin ↑ naloxegol ↑ silodosin ↑ tolvaptan ↑ vorapaxar	Co-administration with finerenone is contraindicated due to the risk of serious adverse effects, including hyperkalemia, hypotension, and hyponatremia. Co-administration with flibanserin is contraindicated due to the risk of serious adverse effects, including hypotension, syncope, and CNS depression. Co-administration with naloxegol is contraindicated due to the risk of opioid withdrawal syndrome. Co-administration with silodosin is contraindicated due to the risk of postural hypotension. Co-administration with tolvaptan is contraindicated due to the risk of dehydration, hypovolemia, and hyperkalemia. Co-administration with vorapaxar is contraindicated due to the potential for serious side effects.

Notes:
[a]INR: international normalized ratio.
[b]Prescribing information for maraviroc.: Available from:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022128Orig1s019,208984Orig1s002lbl.pdf

PAHO/HSS/MT/COVID-19/22-0034

www.paho.org/en

PAHO

Pan American Health Organization

World Health Organization

Americas

PAHO 120th ANNIVERSARY