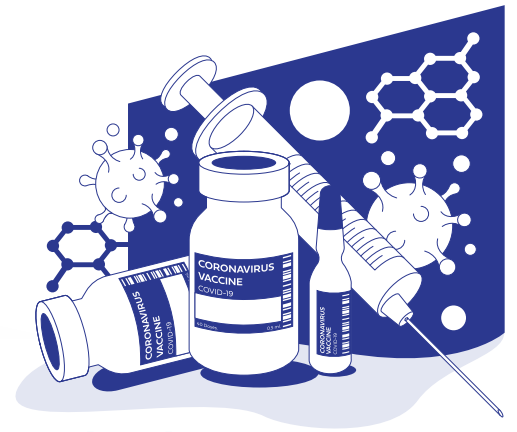


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MINISTRY OF HEALTH  
NATIONAL UNITY GOVERNMENT OF MYANMAR



Interim Guidance for Use of

# Nirmatrelvir/ Ritonavir

in COVID-19 Patients



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Nirmatrelvir/Ritonavir is one of oral antiviral drugs to treat non-severe (mild to moderate) COVID-19 patients.

Although nirmatrelvir is an oral antiviral drug against covid-19 disease, ritonavir has no activity against Covid-19 disease. But ritonavir acts as pharmacokinetic enhancer to prolong the drug level of nirmatrelvir.

In December 2021, it was granted emergency use authorization by the United States' FDA, approved in UK later that month, and in European Union and Canada in January 2022.

In April 2022, WHO made a strong recommendation for nirmatrelvir/ritonavir, sold under the name Paxlovid, for non- severe COVID-19 patients at highest risk of hospital admission, calling it the best therapeutic choice for high-risk patients to date. Currently, generic version of Paxlovid is available around the world.

Treatment of symptomatic Covid-19 with nirmatrelvir plus ritonavir resulted in an 89% lower risk of progression to severe Covid-19 than the risk with placebo, without evident safety concerns (1).

According to observational data, including vaccinated patients, from Israel, United States and Hong Kong, nirmatrelvir/ritonavir is beneficial in high-risk patients :

- **67% reduction in hospitalizations and 81% reduction in deaths compared to the untreated for patients over 65 (2).**
- **45% reduction in hospitalization and greater reductions for obese or unvaccinated patients among adult patients (3)**
- **75% reduction in death compared to non-users (4)**

Clinicians should, however, be aware of drug-to-drug interactions before using nirmatrelvir/ritonavir.

## 2 Initiation of treatment

Nirmatrelvir/ritonavir should be considered in patients with

- age  $\geq$ 12 years AND
- body weight  $\geq$  40 kg AND
- confirmed COVID-19 infection AND
- Within 5 days of onset of symptoms in non-severe patients with at least one high risk factor

**Note:** Before prescribing, drug to drug interactions should be checked.

## 3 Recommendations

If logistical or supply constraints can be overcome, nirmatrelvir/ritonavir is recommended for any eligible individuals.

It is recommended to use the following prioritization strategies when there are logistical or supply constraints:

### Tier-1:

- Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status; or
- Unvaccinated individuals at the highest risk of severe disease (anyone aged  $\geq$ 75 years or anyone aged  $\geq$ 65 years with additional risk factors).

### Tier-2:

- Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged  $\geq$ 65 years or anyone aged  $<$ 65 years with clinical risk factors)

### Tier – 3

- Vaccinated individuals at high risk of severe disease (anyone aged  $\geq 75$  years or anyone aged  $\geq 65$  years with clinical risk factors)

**Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.

### Tier – 4

- Vaccinated individuals at risk of severe disease

**Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.

### Recommendations according to severity

- Use of nirmatrelvir/ritonavir in asymptomatic patients is NOT recommended.
- Use of nirmatrelvir/ritonavir is NOT recommended in non-severe patients who do not have risk factors for disease progression
- Use of nirmatrelvir/ritonavir is recommended in non-severe patients who have risk factors for disease progression.
- Use of nirmatrelvir/ritonavir is NOT recommended in severe or critical patients .

**Note:** Risks factors for severe COVID-19 disease are as follows:

Diabetes, overweight (BMI  $>25$ ), chronic lung disease, chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, and patients  $>60$  years

## 4 Dose

Nirmatrelvir 300 mg with ritonavir 100 mg, administered together, twice daily for 5 days; initiate as soon as possible after COVID-19 diagnosis, and within 5 days of symptom onset.

## 5 Administration

Administered orally with or without food.

Swallow tablets whole; do not chew, break, or crush.

Nirmatrelvir must be co-administered with ritonavir; failure to correctly co-administer may result in insufficient plasma levels.

## 6 Dosing adjustment in liver and renal impairment

| Renal impairment  |   |                 | Liver impairment  |                    |
|---|---|-----------------|---|--------------------|
| eGFR $\geq$ 60 mL/min   | eGFR $\geq$ 30 to <60 mL/min  | eGFR <30 mL/min | Child-Pugh Class A or B   | Child-Pugh Class C |
| Nirmatrelvir 300 mg with ritonavir 100 mg PO twice daily for 5 days | Nirmatrelvir 150 mg with ritonavir 100 mg PO twice daily for 5 days | Not recommended | Nirmatrelvir 300 mg with ritonavir 100 mg PO twice daily for 5 days | Not recommended    |

## 7 Adverse Reactions (5)

|                            |  |
|----------------------------|--|
| Cardiovascular             | Hypertension   |
| Dermatology                | Pruritus, skin rash, Stevens-Johnson syndrome (with ritonavir), toxic epidermal necrolysis (with ritonavir), urticaria |
| Gastrointestinal           | Diarrhea, dysgeusia, abdominal pain, nausea, malaise   |
| Hepatology                 | Anaphylaxis (with ritonavir), angioedema   |
| Neuromuscular and skeletal | Myalgia  |
| Respiratory                | Dyspnea  |

## 8 Contraindications (5)

- Significant hypersensitivity (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome) to nirmatrelvir, ritonavir, or any component of the formulation
- Coadministration with drugs that are highly dependent on CYP3A for clearance, and for which elevated concentrations are associated with serious and/or life-threatening reactions (e.g., alfuzosin, amiodarone, clozapine, colchicine, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, finerenone, flecainide, flibanserin, ivabradine, lomitapide, lovastatin, lurasidone, methylergonovine, midazolam [oral], naloxegol, pethidine, pimozide, propafenone, quinidine, ranolazine, sildenafil [when used for the treatment of pulmonary arterial hypertension], silodosin, simvastatin, tolvaptan, triazolam, ubrogepant, voclosporin)
- Coadministration with strong CYP3A inducers
- Coadministration with ergonovine, fusidic acid, neratinib, rivaroxaban, salmeterol, vardenafil, venetoclax, voriconazole

## 9 Pregnancy (5)

Pregnancy is a risk factor for severe COVID-19; the use of nirmatrelvir/ritonavir may be offered to pregnant and recently pregnant patients.

Use may be considered in non-hospitalized, COVID-19–positive, pregnant patients who have mild to moderate symptoms, especially patients with one or more additional risk factors.

## 10 Lactation (5)

Excretion of nirmatrelvir is unknown but ritonavir is present in breast milk.

Lactation is not a contraindication for use.

The decision to breastfeed during therapy should be considered for the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.

# 11 Drug to drug interaction (5)

Nirmatrelvir/ritonavir has significant and complex drug-to-drug interaction, primarily due to the ritonavir component of the combination.

Before prescribing ritonavir-boosted nirmatrelvir, **clinicians should carefully review the patient's concomitant medications, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.**



A quick reference tables to check drug-to-drug interactions with nirmatrelvir/ritonavir

## Medications Without Clinically Relevant Interactions

*These commonly prescribed drugs may be co-administered without dose adjustment and without increased monitoring. This list cannot cover for each drug category.*

### Acid reducing agents

- Famotidine
- Omeprazole
- Pantoprazole

### Allergy medications

- Cetirizine
- Diphenhydramine
- Loratadine

### Anti-infective agents

- Azithromycin
- Hydroxychloroquine

### Cardiovascular agents

- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide Dinitrate
- Lisinopril
- Losartan
- Metoprolol
- Prasugrel

### Diabetes medications

- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

### Immunosuppressants

- Methotrexate
- Mycophenolate
- Prednisone

### Lipid-modifying agents

- Ezetimibe
- Pitavastatin
- Pravastatin

### Neuropsychiatric agents

- Amitriptyline
- Bupropion
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline
- Venlafaxine

### Pain medications

- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Naproxen

### Respiratory medications

- Corticosteroids (inhaled)
- Formoterol
- Montelukast

### Miscellaneous

- Allopurinol
- Contraceptives (oral)
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine
- Ondansetron

## Prescribe Alternative COVID-19 Therapy

*For these drugs, management strategies are not possible or feasible, or the risks outweigh the potential benefits.*

*If the patient is on any of the following drugs, alternative therapy for COVID-19 such as Molnupiravir or Remdesivir should be considered.*

### Anticonvulsants

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

### Anti-infective agents

- Glecaprevir/  
pibrentasvir
- Rifampin
- Rifapentine

### Immunosuppressants

- Voclosporin

### Cardiovascular agents

- Amiodarone
- Clopidogrel
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine
- Propafenone
- Quinidine

### Neuropsychiatric agents

- Clozapine
- Lumateperone
- Lurasidone
- Midazolam (oral)
- Pimozide

### Pain medications

- Meperidine  
(pethidine)

### Pulmonary hypertension medications

- Sildenafil
- Tadalafil
- Vardenafil

### Miscellaneous

- Bosentan
- Certain  
chemotherapeutic  
agents
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan

## Temporarily Withhold Concomitant Medication, If Clinically Appropriate

*Withhold these drugs during nirmatrelvir/ritonavir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for an extended period if the patient is elderly or the drug has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.*

### Anticoagulants

- Rivaroxaban

### Anti-infective agents

- Erythromycin

### BPH medications

- Alfuzosin
- Silodosin

### Cardiovascular agents

- Aliskiren
- Ranolazine
- Ticagrelor
- Vorapaxar

### Immunosuppressants

- Everolimus
- Sirolimus
- Tacrolimus

### Lipid-modifying agents

- Atorvastatin
- Lomitapide
- Lovastatin
- Rosuvastatin
- Simvastatin

### Migraine medications

- Eletriptan
- Rimegepant
- Ubrogapant

### Neuropsychiatric agents

- Clonazepam
- Clorazepate
- Diazepam
- Estazolam
- Flurazepam
- Suvorexant
- Triazolam

### Erectile dysfunction medications

- Avanafil

### Respiratory medications

- Salmeterol

### Miscellaneous

- Certain chemotherapeutic agents
- Colchicine
- Finerenone
- Flibanserin
- Naloxegol

## Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the [Liverpool COVID-19 Drug Interactions website](#) or the [Ontario COVID-19 Science Advisory Table](#) for specific dosing recommendations. If the dose of the concomitant drug cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant drug or COVID-19 therapy.

### Anticoagulants

- Apixaban
- Dabigatran
- Edoxaban

### Anti-infective agents

- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin

### BPH medications

- Tamsulosin

### Cardiovascular agents

- Cilostazol
- Digoxin
- Mexiletine

### Diabetes medications

- Saxagliptin
- Erectile

### dysfunction medications

- Sildenafil
- Tadalafil
- Vardenafil

### Immunosuppressants

- Cyclosporine

### Neuropsychiatric agents

- Alprazolam
- Aripiprazole
- Brexpiprazole
- Buspirone
- Cariprazine
- Chlordiazepoxide
- Clobazam
- Iloperidone
- Pimavanserin
- Quetiapine
- Trazodone

### Pain medications

- Fentanyl
- Hydrocodone
- Oxycodone

### Pulmonary hypertension medications

- Riociguat

### Miscellaneous

- Certain chemotherapeutic agents
- Darifenacin
- Elexacaftor/tezacaftor/ivacaftor
- Eluxadoline
- Ivacaftor
- Tezacaftor/ivacaftor

## Continue Concomitant Medication and Monitor for Adverse Effects

Pre-emptive dose adjustment is not required but may be considered. Educate patients on potential adverse effects. Consult the [Liverpool COVID-19 Drug Interactions website](#) or the [Ontario COVID-19 Science Advisory Table](#) for monitoring guidance and dose adjustment information if needed.

### Anticoagulants

- Warfarin

### Anti-infective agents

- Cobicistat or ritonavir-boosted antiretrovirals
- Isavuconazole
- Posaconazole
- Voriconazole

### BPH medications

- Doxazosin
- Terazosin

### Diabetes medications

- Glyburide

### Cardiovascular agents

- Amlodipine
- Diltiazem
- Felodipine
- Nifedipine
- Sacubitril
- Valsartan
- Verapamil

### Neuropsychiatric agents

- Haloperidol
- Hydroxyzine
- Mirtazapine
- Risperidone
- Ziprasidone
- Zolpidem

### Pain medications

- Buprenorphine
- Hydromorphone
- Methadone
- Morphine
- Tramadol

## 12 Covid-19 rebound

Recurrent symptoms of covid-19 have been observed between 2-8 days after completing a 5-day course of nirmatrelvir/ritonavir (5) as well as in cases treated with molnupiravir (6).

The frequency, mechanism, and clinical implications of these events are unclear.

It is characterized by milder and brief symptom development and viral detection. Repetition of antiviral treatment is not necessary. Therefore, concerns about the recurrence of symptoms should not be a reason to avoid using nirmatrelvir/ritonavir. However, isolation of patients and wearing of masks are still needed.

# 13

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