Safety and monitoring for patients receiving Nirmatrelvir-ritonavir for **COVID-19**

Guidance for health care workers

SAFETY AND GENERAL MONITORING

Prior to starting nirmatrelvir-ritonavir

- If clinically indicated, test for HIV. In the event of a primary diagnosis of HIV-1, treatment with nirmatrelvir-ritonavir should be at the health care worker's discretion (see adverse effects and drug interactions) and referrals for further HIV care initiated.
- If clinically indicated, evaluate for pregnancy.
  – If pregnant, the patient should not be treated with nirmatrelvir-ritonavir.
- Review any concomitant medications and check for potential for drug interactions prior to and during therapy. Nirmatrelvir-ritonavir is known to affect the CYP3A enzyme that is responsible for the metabolism of various other medicines (see contraindications and drug interactions below).

During treatment

- Advise patients taking nirmatrelvir-ritonavir to monitor for any side-effects (see below).

If the patient is unable to tolerate nirmatrelvir-ritonavir they should be instructed to immediately contact their health care worker before discontinuation of treatment.

Drug interactions

- Initiation of nirmatrelvir-ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving nirmatrelvir-ritonavir, may increase plasma concentrations of medications metabolized by CYP3A.
- Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of nirmatrelvir-ritonavir, respectively.
- These interactions may lead to:
  — Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
  — Clinically significant adverse reactions from greater exposures of nirmatrelvir-ritonavir.
  — Loss of therapeutic effect of nirmatrelvir-ritonavir and possible development of viral resistance.

See list of all possible interactions at: **FDA fact sheet https://www.fda.gov/media/155050/download** as well at the University of Liverpool drug interactions checker (https://www.covid19-druginteractions.org).

Adverse effects

- Side-effects are rare and include dysgeusia, diarrhoea, hypertension and myalgias.
- **Hepatotoxicity** has also been reported. In patients receiving ritonavir, hepatic transaminase elevations, clinical hepatitis and jaundice have occurred.

Hypersensitivity and allergic reactions

- Hypersensitivity reactions, although rare, have been reported, and include urticaria, angioedema, dyspnoea, mild skin eruptions and pruritis.
- Anaphylaxis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) have been reported with ritonavir, which is co-administered with nirmatrelvir.
- Advise your patient that if signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue the medications and contact their health care provider for appropriate medical care.

Antiviral resistance

- Data are currently insufficient to ascertain how high the barrier of resistance is with SARS-CoV-2 to nirmatrelvir-ritonavir. Based on experience with other similar types of antivirals, the drug will place a selective pressure for resistance mutations within individuals, with the potential to spread to the population.

Risk of HIV-1 resistance

- Nirmatrelvir is co-administered with ritonavir, which may increase the risk of patients with **uncontrolled or undiagnosed** HIV developing resistance to protease inhibitors.

World Health Organization

For detailed information, see WHO *Therapeutics and COVID-19: living guideline*. https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics

COVID-19 CLINICAL CARE PATHWAY

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Nirmatrelvir-ritonavir for **COVID-19**

SAFETY AND GENERAL MONITORING

Medicinal products that are **contraindicated** for concomitant use with nirmatrelvir-ritonavir

Medicinal product class	Medicinal products within class	Clinical comments
Interactions that result in increased concentrations of concomitant medicinal product as nirmatrelvir-ritonavir inhibits their CYP3A4 metabolic pathway		
Alpha 1-adrenoreceptor antagonist	alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension.
Analgesics	pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities.
Antianginal	ranolazine	Potentially increased plasma concentrations of ranolazine may result in serious and/or life-threatening reactions.
Anticancer	neratinib, venetoclax	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity. Increased plasma concentrations of venetoclax which may increase the risk of tumour lysis syndrome at the dose initiation and during the dose-titration phase.
Antiarrhythmics	amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Potentially increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone and quinidine may result in arrhythmias or other serious adverse effects.
Antibiotic	fusidic acid	Increased plasma concentrations of fusidic acid and ritonavir.
Anti-gout	colchicine	Increased plasma concentrations of colchicine may result in serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antihistamines	astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine may result in serious arrhythmias from these agents.
Antipsychotics/neuroleptics	lurasidone, pimozide, clozapine, quetiapine	Increased plasma concentrations of lurasidone, pimozide and clozapine may result in serious and/or life-threatening reactions. Increased plasma concentrations of quetiapine may lead to coma.
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
GI motility agent	cisapride	Increased plasma concentrations of cisapride, thereby increasing the risk of serious arrhythmias from this agent.
Lipid-modifying agents HMG-CoA reductase inhibitors Microsomal triglyceride transfer protein (MTTP) inhibitor	lovastatin, simvastatin lomitapide	Increased plasma concentrations of lovastatin and simvastatin resulting in increased risk of myopathy, including rhabdomyolysis. Increased plasma concentrations of lomitapide.
PDE5 inhibitors	avanafil, vardenafil sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)	Increased plasma concentrations of avanafil and vardenafil. Increased plasma concentrations of sildenafil can potentially result in visual abnormalities, hypotension, prolonged erection and syncope.
Sedative/hypnotics	clonazepam, diazepam, estazolam, flurazepam, triazolam, oral midazolam	Increased plasma concentrations of clonazepam, diazepam, estazolam, flurazepam, triazolam and oral midazolam can increase risk of extreme sedation and respiratory depression.
Interactions that result in decreased concentrations of nirmatrelvir-ritonavir as the concomitant medicinal products induce nirmatrelvir-ritonavir's CYP3A4 metabolic pathway		
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin	Decreased plasma concentrations of nirmatrelvir-ritonavir may lead to loss of virologic response and possible resistance.
Antimycobacterials	rifampin	Potentially decreased plasma concentrations of nirmatrelvir-ritonavir may lead to loss of virologic response and possible resistance.
Herbal products	St John's Wort (Hypericum perforatum)	Potentially decreased plasma concentrations of nirmatrelvir-ritonavir may lead to loss of virologic response and possible resistance.

Source: Summary of Product Characteristics for Paxlovid - GOV.UK (www.gov.uk)

For further information, please reference the United States Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA) fact sheets on nirmaltrevir-ritonavir:

- FDA: https://www.fda.gov/media/155050/download
- MHRA: https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid
- EMA: https://www.ema.europa.eu/en/documents/referral/paxlovid-pf-07321332-ritonavir-covid-19-article-53-procedure-conditions-use-conditions-distribution_en.pdf

World Health Organization

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