Generic Name: Nirmatrelvir/Ritonavir
Trade Name: Paxlovid
UKSPC Effective Date: October 19, 2022
Supersedes: August 19, 2022
Approved by BPOM: May 15, 2023

# FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF PAXLOVID

Badan POM, the Indonesia Food and Drug Administration, has issued an Emergency Use Authorization (EUA) to permit the emergency use of Paxlovid. Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

The Emergency Use Authorization of Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

**ADMINISTRATION:**

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets.

Nirmatrelvir must be coadministered with ritonavir. Failure to correctly coadminister nirmatrelvir with ritonavir will result in plasma concentrations of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.

The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days. Paxlovid should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms.

Medical condition associated with an increased risk of developing severe illness from COVID-19 including:
- ≥ 60 years of age
- BMI > 25
- Current smoker and history of at least 100 lifetime cigarettes
- Immunosuppressive disease or prolonged use of immune weakening medications
- Chronic lung disease
- Hypertension
- Cardiovascular disease
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease
- Sickle cell disease

Paxlovid can be taken with or without food. The tablets should be swallowed whole and not chewed, broken or crushed.

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to Paxlovid.

For information on clinical trials that are testing the use of Paxlovid, please see https://clinicaltrials.gov/ and https://trialsearch.who.int/.

## INSTRUCTION FOR ADMINISTRATION

This section provides essential information on the use of Paxlovid for treatment of laboratory confirmed coronavirus disease 2019 (COVID-19).

## COMPOSITION

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets.

Each pink nirmatrelvir film-coated tablet contains 150 mg of nirmatrelvir.

Each white ritonavir film-coated tablet contains 100 mg of ritonavir.

Excipients with known effect
Each nirmatrelvir 150 mg film-coated tablet contains 176 mg of lactose.

**Excipients**
Nirmatrelvir
Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate
Film-coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Iron oxide red (E172)

Ritonavir
Tablet core:
Copovidone
Sorbitan laurate
Silica colloidal anhydrous (E551)
Calcium hydrogen phosphate anhydrous
Sodium stearyl fumarate
Film-coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Hydroxypropyl cellulose (E463)
Talc (E553b)
Silica colloidal anhydrous (E551)
Polysorbate 80 (E433)

## INDICATIONS

Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

## CONTRAINDICATIONS

Paxlovid is contraindicated in patients:

- with a history of clinically significant hypersensitivity to the active substances (nirmatrelvir /ritonavir) or to any of the excipients listed in **COMPOSITION**.
- with severe hepatic impairment.
- with severe renal impairment.

Paxlovid is also contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. Paxlovid is also contraindicated with medicinal products that are potent CYP3A inducers where significantly reduced plasma nirmatrelvir /ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance.

**Table 1: 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 Paxlovid 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 | Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity. |
| | venetoclax | Increased plasma concentrations of venetoclax which may increase the risk risk of tumour lysis syndrome at the dose initiation and during the dose-titration phase. |
| Antiarrhythmics | amiodarone, bepridil, dronedarone, encainide, flecainide, | Potentially increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone and quinidine may result in |

**Table 1: Medicinal products that are contraindicated for concomitant use with nirmatrelvir /ritonavir**

| Medicinal product class | Medicinal products within class | Clinical comments |
|---|---|---|
| | propafenone, quinidine | 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 | Increased plasma concentrations of lurasidone, pimozide and clozapine may result in serious and/or life-threatening reactions. |
| | quetiapine | 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<br><br>HMG-CoA reductase inhibitors | lovastatin, simvastatin | Increased plasma concentrations of lovastatin and simvastatin resulting in increased risk of myopathy, including rhabdomyolysis. |
| Microsomal triglyceride transfer protein (MTTP) inhibitor | lomitapide | Increased plasma concentrations of lomitapide. |
| PDE5 inhibitors | avanafil, vardenafil | Increased plasma concentrations of avanafil and vardenafil. |
| | sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH) | 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[a] | Increased plasma concentrations of clonazepam, diazepam, estazolam, flurazepam, triazolam and oral midazolam can increase risk of extreme sedation and respiratory depression. |

**Table 1: Medicinal products that are contraindicated for concomitant use with nirmatrelvir /ritonavir**

| Medicinal product class | Medicinal products within class | Clinical comments |
|---|---|---|
| **Interactions that result in decreased concentrations of nirmatrelvir/ritonavir as the concomitant medicinal products induce Paxlovid's CYP3A4 metabolic pathway** | | |
| Anticancer | apalutamide | Decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance. |
| 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. |

a. See **Pharmacokinetic properties**, Interaction studies conducted with nirmatrelvir /ritonavir.

## DOSAGE AND ADMINISTRATION

**Paxlovid must be administered by a healthcare professional pursuant to a valid prescription of a licensed practitioner.**

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*Posology*

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- Sickle cell disease

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A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

*Special populations*

*Paediatric population*
The safety and efficacy of Paxlovid in paediatric patients younger than 18 years of age have not yet been established.

*Elderly*
No dose adjustment is currently recommended for elderly patients.

*Renal impairment*
No dose adjustment is needed in patients with mild renal impairment.

In patients with moderate renal impairment, the dose of Paxlovid should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements.

Paxlovid is not recommended in patients with severe renal impairment or with renal failure as the appropriate dose has not yet been determined (see **Pharmacokinetic properties**).

*Hepatic impairment*
No dosage adjustment of Paxlovid is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, Paxlovid is contraindicated in patients with severe hepatic impairment.

*Concomitant therapy with ritonavir- or cobicistat-containing regimen*
No dose adjustment is needed; the dose of Paxlovid is 300 mg/100 mg twice daily for 5 days.

Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Risk of serious adverse reactions due to interactions with other medicinal products

Initiation of Paxlovid, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving Paxlovid, may increase plasma concentrations of medicinal products metabolised by CYP3A.

Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of Paxlovid.
- Loss of therapeutic effect of Paxlovid and possible development of viral resistance.

See Table 1 for medicinal products that are contraindicated for concomitant use with nirmatrelvir/ritonavir (see **CONTRAINDICATIONS**) and Table 2 for potentially significant interactions with other medicinal products (see **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**). Potential for interactions should be considered with other medicinal products prior to and during Paxlovid therapy; concomitant medicinal products should be reviewed during Paxlovid therapy and the patient should be monitored for the adverse reactions associated with the concomitant medicinal products. The risk of interactions with concomitant medications during the 5-day treatment period for Paxlovid should be weighed against the risk of not receiving Paxlovid.

Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

HIV resistance

As nirmatrelvir is coadministered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Excipients

Nirmatrelvir tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Nirmatrelvir and ritonavir tablets each contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

## INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Paxlovid (Nirmatrelvir/ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when coadministered with nirmatrelvir/ritonavir. Thus, coadministration of nirmatrelvir/ritonavir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see Table 1, **CONTRAINDICATIONS**).

*In vitro* study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8, and CYP2C9. The clinical relevance is unknown. Based on *in vitro* data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Ritonavir also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Coadministration of other CYP3A4 substrates that may lead to potentially significant interaction should be considered only if the benefits outweigh the risks (see Table 2).

Nirmatrelvir/ritonavir is a CYP3A substrate; therefore, medicinal products that induce CYP3A may decrease plasma concentrations of Nirmatrelvir and ritonavir and reduce Paxlovid therapeutic effect.

Medicinal products listed in Table 1 (section **CONTRAINDICATIONS**) and Table 2 are a guide and not considered a comprehensive list of all possible medicinal products that may interact with Nirmatrelvir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

**Table 2: Interaction with other medicinal products and other forms of interaction**

| **Medicinal product class** | **Medicinal product within class (AUC change, $C_{max}$ Change)** | **Clinical comments** |
|---|---|---|
| α1-adrenoreceptor antagonist | ↑alfuzosin | Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see **CONTRAINDICATIONS**). |
| Amphetamine derivatives | ↑methylphenidate, ↑dexamfetamine | Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are coadministered with Paxlovid. |
| Analgesics | ↑buprenorphine (57%, 77%), ↑norbuprenorphine (33%, 108%) | The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when the two are dosed together. |
| | ↑pethidine, ↑piroxicam, ↑propoxyphene | Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities (see **CONTRAINDICATIONS**). |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | ↑fentanyl | Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir. |
| | ↓methadone (36%, 38%) | Increased methadone dose may be necessary when coadministered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy. |
| | ↓morphine | Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir dosed as a pharmacokinetic enhancer. |
| Antianginal | ↑ranolazine | Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see **CONTRAINDICATIONS**). |
| Antiarrhythmics | ↑amiodarone, ↑dronedarone, ↑flecainide, ↑propafenone, ↑quinidine | Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and is therefore contraindicated (see **CONTRAINDICATIONS**). |
| | ↑digoxin | This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer. |
| Antiasthmatic | ↓theophylline (43%, 32%) | An increased dose of theophylline may be required when coadministered with ritonavir, due to induction of CYP1A2. |
| Anticancer agents | ↑afatinib | Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and Cmax depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with Paxlovid (refer to the afatinib Product |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | | information). Monitor for ADRs related to afatinib. |
| | ↑abemaciclib | Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Coadministration of abemaciclib and Paxlovid should be avoided. If this coadministration is judged unavoidable, refer to the abemaciclib Product information for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib. |
| | ↑apalutamide | Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of Nirmatrelvir/ritonavir and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when coadministered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of Paxlovid with apalutamide is contraindicated. |
| | ↑ceritinib | Serum concentrations of ceritinib may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with Paxlovid. Refer to the ceritinib Product information for dosage adjustment recommendations. Monitor for ADRs related to ceritinib. |
| | ↑dasatinib, ↑nilotinib, ↑vincristine, ↑vinblastine | Serum concentrations may be increased when coadministered with ritonavir resulting in the potential for increased incidence of adverse events. |
| | ↑encorafenib | Serum concentrations of encorafenib may be increased when coadministered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Coadministration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety. |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | ↑fostamatinib | Coadministration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Refer to the fostamatinib Product information for dose reduction recommendations if such events occur. |
| | ↑ibrutinib | Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumour lysis syndrome. Coadministration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity. |
| | ↑neratinib | Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with Paxlovid is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see **CONTRAINDICATIONS**). |
| | ↑venetoclax | Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase (see **CONTRAINDICATIONS** and refer to the venetoclax Product information). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax Product information for dosing instructions). |
| Anticoagulants | ↑apixaban, ↑dabigatran[a] (194%, 233%) | Potentially increased apixaban and dabigatran concentrations which may lead to an increased bleeding risk. Refer to apixaban and dabigatran Product information for further information. |
| | ↑rivaroxaban (153%, 53%) | Inhibition of CYP3A and P-gp lead to increased plasma levels and |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | | pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban. |
| | ↑vorapaxar | Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The coadministration of vorapaxar with Paxlovid is not recommended (refer to the vorapaxar Product information). |
| | warfarin,<br>↑↓S-warfarin (9%, 9%),<br>↓↔R-warfarin (33%) | Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when coadministered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is coadministered with ritonavir. |
| Anticonvulsants | carbamazepine[a] | Carbamazepine is strong CYP3A4 inducer, and this may lead to a decreased exposure of nirmatrelvir and ritonavir and potential loss of virologic response. Concomitant use of carbamazepine with Paxlovid is contraindicated (see **CONTRAINDICATIONS**). |
| | ↓divalproex, ↓lamotrigine, ↓phenytoin | Ritonavir dosed as a pharmacokinetic enhancer induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are coadministered with ritonavir. Phenytoin may decrease serum levels of ritonavir. |
| Antidepressants | ↑amitriptyline, ↑fluoxetine, ↑imipramine, ↑nortriptyline, ↑paroxetine, ↑sertraline | Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir. |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | ↑desipramine (145%, 22%) | The AUC and $C_{max}$ of the 2-hydroxy metabolite were decreased 15% and 67%, respectively. Dosage reduction of desipramine is recommended when coadministered with ritonavir. |
| Anti-gout | ↑colchicine | Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with Paxlovid is contraindicated (see **CONTRAINDICATIONS**). |
| Antihistamines | ↑fexofenadine | Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. |
| | ↑loratadine | Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is coadministered with ritonavir. |
| Anti-infectives | ↑fusidic acid | Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see **CONTRAINDICATIONS**). |
| | ↑rifabutin (4-fold, 2.5-fold)<br>↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold) | Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when coadministered with ritonavir as a pharmacokinetic enhancer. |
| | rifampicin | Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. Concomitant use of rifampicin with Paxlovid is contraindicated (see **CONTRAINDICATIONS**). |
| | ↓voriconazole (39%, 24%) | Coadministration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | ↑ketoconazole (3.4-fold, 55%) | Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when coadministered with ritonavir. |
| | ↑itraconazole[a], ↑erythromycin | Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is coadministered with ritonavir. |
| | ↓atovaquone | Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is coadministered with ritonavir. |
| | ↑bedaquiline | No interaction study is available with ritonavir only. Due to the risk of bedaquiline related adverse events, coadministration should be avoided. If the benefit outweighs the risk, coadministration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline Product information). |
| | delamanid | No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if coadministration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | | period is recommended (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and refer to the delamanid Product information). |
| | ↑clarithromycin (77%, 31%)<br>↓14-OH clarithromycin metabolite (100%, 99%) | Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be coadministered with ritonavir dosed as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%. |
| | sulfamethoxazole/trimethoprim | Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary. |

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|---|---|---|
| Anti-HIV protease inhibitors | ↑amprenavir (64%, 5-fold) | Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the Product information for amprenavir. |
| | ↑atazanavir (86%, 11-fold) | Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the Product information for atazanavir. |
| | ↑darunavir (14-fold) | Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. For further information, refer to the Product information for darunavir. |
| | ↑fosamprenavir (2.4-fold, 11-fold) measured as amprenavir) | Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. For further information, physicians should refer to the Product information for fosamprenavir. |
| Anti-HIV | ↑efavirenz (21%) | A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is coadministered with ritonavir. |
| | ↑maraviroc (161%, 28%) | Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the Product information for maraviroc. |
| | ↓raltegravir (16%, 1%) | Coadministration of ritonavir and raltegravir results in a minor reduction in raltegravir levels |
| | ↓zidovudine (25%, ND) | Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary. |
| Antipsychotics | ↑clozapine, ↑pimozide | Ritonavir coadministration is likely to result in increased plasma concentrations |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | | of clozapine or pimozide and is therefore contraindicated (see **CONTRAINDICATIONS**). |
| | ↑haloperidol, ↑risperidone, ↑thioridazine | Ritonavir is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir. |
| | ↑lurasidone | Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see **CONTRAINDICATIONS**). |
| | ↑quetiapine | Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of Paxlovid and quetiapine is contraindicated as it may increase quetiapine-related toxicity (see **CONTRAINDICATIONS**). |
| β2-agonist (long acting) | ↑salmeterol | Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected. Therefore, concomitant use is not recommended. |
| Calcium channel antagonist | ↑amlodipine, ↑diltiazem, ↑nifedipine | Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir. |
| Endothelin Antagonists | ↑bosentan | Coadministration of bosentan and ritonavir may increase steady-state bosentan $C_{max}$ and AUC. |
| | ↑riociguat | Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The coadministration of riociguat with Paxlovid is not recommended (refer to riociguat Product information). |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| Ergot Derivatives | ↑dihydroergotamine, ↑ergonovine, ↑ergotamine, ↑methylergonovine | Ritonavir coadministration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see **CONTRAINDICATIONS**) |
| HCV Direct Acting Antiviral | ↑glecaprevir/pibrentasvir | Serum concentrations may be increased due to P-gp, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and Paxlovid is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure. |
| HMG Co-A Reductase | ↑lovastatin, ↑simvastatin | HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see **CONTRAINDICATIONS**). |
| | ↑atorvastatin, ↑fluvastatin, ↑pravastatin, ↑rosuvastatin, | Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended. |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| **Medicinal product class** | **Medicinal product within class (AUC change, $C_{max}$ Change)** | **Clinical comments** |
|---|---|---|
| Hormonal Contraceptive | ↓ethinylestradiol (40%, 32%) | Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives. |
| Immunosuppressants | ↑cyclosporine, ↑tacrolimus, ↑everolimus | Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir. |
| Lipid-modifying agents | ↑lomitapide | CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of Paxlovid with lomitapide is contraindicated (see Product information for lomitapide) (see **CONTRAINDICATIONS**). |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| Phosphodiesterase (PDE5) Inhibitors | ↑avanafil (13-fold, 2.4-fold) | Concomitant use of avanafil with Paxlovid is contraindicated (see **CONTRAINDICATIONS**). |
| | ↑sildenafil (11-fold, 4-fold) | Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours. Concomitant use of sildenafil with Paxlovid is contraindicated in pulmonary arterial hypertension patients (see **CONTRAINDICATIONS**). |
| | ↑tadalafil (124%, ↔) | The concomitant use of tadalafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions. |
| | ↑vardenafil (49-fold, 13-fold) | Concomitant use of vardenafil with Paxlovid is contraindicated (see **CONTRAINDICATIONS**). |
| Sedatives/hypnotics | ↑clonazepam, ↑diazepam, ↑estazolam, ↑flurazepam | Ritonavir coadministration is likely to result in increased plasma concentrations of clonazepam, diazepam, estazolam and flurazepam and is therefore contraindicated (see **CONTRAINDICATIONS**). |
| | ↑oral (1430%, 368%) and parenteral midazolam[a] | Midazolam is extensively metabolised by CYP3A4. Coadministration with Paxlovid may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, Paxlovid should not be coadministered with orally administered midazolam (see **CONTRAINDICATIONS**), whereas caution should be used with coadministration of Paxlovid and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggests a possible 3 – 4-fold increase in midazolam plasma levels. If Paxlovid is |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | | coadministered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered. |
| | ↑triazolam (> 20-fold, 87%) | Ritonavir coadministration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see **CONTRAINDICATIONS**) |
| | ↓pethidine (62%, 59%), ↑norpethidine metabolite (47%, 87%) | The use of pethidine and ritonavir is contraindicated due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (e.g., seizures) (see **CONTRAINDICATIONS**). |
| | ↑alprazolam (2.5-fold, ↔) | Alprazolam metabolism is inhibited following the introduction of ritonavir. Caution is warranted during the first several days when alprazolam is coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops. |
| | ↑buspirone | Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir. |
| Sleeping agent | ↑zolpidem (28%, 22%) | Zolpidem and ritonavir may be coadministered with careful monitoring for excessive sedative effects. |
| Smoke cessation | ↓bupropion (22%, 21%) | Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | | induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit CYP2B6 *in vitro*, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting reductions in bupropion concentrations may have onset several days after initiation of ritonavir coadministration. |
| Steroids | Inhaled, injectable or intranasal fluticasone propionate, budesonide, triamcinolone | Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86%) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A e.g., budesonide and triamcinolone. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period. |
| | ↑dexamethasone | Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir. |
| | ↑prednisolone (28%, 9%) | Careful monitoring of therapeutic and adverse effects is recommended when |

**Table 2: Interaction with other medicinal products and other forms of interaction**

| Medicinal product class | Medicinal product within class (AUC change, $C_{max}$ Change) | Clinical comments |
|---|---|---|
| | | prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively. |
| Thyroid hormone replacement therapy | levothyroxine | Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment. |

Abbreviations: ATL=alanine aminotransferase, AUC= area under the curve; $C_{max}$= maximum concentrations.
a. See **Pharmacokinetic properties**, Interaction studies conducted with nirmatrelvir/ritonavir.

## FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential/Contraception in males and females

There are no human data on the use of Paxlovid during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid and as a precautionary measure until after one full menstrual cycle is completed after stopping Paxlovid treatment.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping Paxlovid (see **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Pregnancy

There are no data from the use of Paxlovid in pregnant women. Paxlovid is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

There was no nirmatrelvir-related effect on foetal morphology or embryo-foetal viability at any dose tested in rat or rabbit embryo-foetal developmental toxicity studies (see **Preclinical safety data**).

A large number of pregnant women were exposed to ritonavir during pregnancy. These data largely refer to exposures where ritonavir was used in combination therapy and not at therapeutic ritonavir doses but at lower doses as a pharmacokinetic enhancer for other protease inhibitors, similar to the ritonavir dose used for nirmatrelvir/ritonavir. These data indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. Animal data with ritonavir have shown reproductive toxicity (see **Preclinical safety data**).

Breast-feeding

There are no human data on the use of Paxlovid in breast-feeding.

It is unknown whether nirmatrelvir is excreted in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Paxlovid and for 7 days after the last dose of Paxlovid.

Fertility

There are no human data on the effect of Paxlovid on fertility. No human data on the effect of nirmatrelvir on fertility are available. Nirmatrelvir produced no effects on fertility in rats (see **Preclinical safety data**).

There are no human data on the effect of ritonavir on fertility. Ritonavir produced no effects on fertility in rats.

## EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no clinical studies that evaluated the effects of Paxlovid on ability to drive and use machines.

## UNDESIRABLE EFFECT

Summary of the safety profile

The safety of Paxlovid is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomised, placebo-controlled trial in non-hospitalised adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection (see **Pharmacodynamic properties**). A total of 2,224 symptomatic adult participants 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) (n=1109) or placebo (n=1115). Study drugs were to be taken twice daily for up to 5 days.

Adverse reactions in the Paxlovid group (≥ 1%) that occurred at a greater frequency than in the placebo group were dysgeusia (5.6% and 0.3%, respectively), diarrhoea (3.1% and 1.6%), vomiting (1.1% and 0.8%), and headache (1.4% and 1.3%).

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (frequency cannot be estimated from the available data).

**Table 3: Adverse reactions with Paxlovid**

| System organ class | Frequency category | Adverse reactions |
|---|---|---|
| Immune system disorders | Common | Hypersensitivity |
| Nervous system disorders | Common | Dysgeusia, headache |
| Gastrointestinal disorders | Common | Diarrhoea, vomiting |

Paediatric population

The safety and efficacy of Paxlovid in paediatric patients have not been established.

**Reporting of suspected adverse reactions**
Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs.

Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (see **MANDATORY REQUIREMENTS FOR PAXOLOVID ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION**).

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties
Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: not yet assigned.

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS-CoV-2 3CL protease. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Nirmatrelvir was shown to be a potent inhibitor of SARS-CoV-2 3CL protease (Ki=0.00311 μM or $IC_{50}$=0.0192 μM) in a biochemical enzymatic assay.

Ritonavir is not active against SARS-CoV-2 3CL protease. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

Antiviral activity

*In vitro antiviral activity*
Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line ($EC_{50}$ value of 61.8 nM and $EC_{90}$ value of 181 nM) after 3 days of drug exposure. Nirmatrelvir had cell culture antiviral activity (with $EC_{50}$ values in the low nano molar range ≤ 3-fold relative to USA-WA1/2020) 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 with approximately 3.3-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

*In vivo antiviral activity*
Nirmatrelvir showed antiviral activity in mouse models with mouse-adapted SAR-CoV-2 infection in BALB/c and 129 mouse strains. Oral administration of nirmatrelvir at 300 mg/kg or 1,000 mg/kg twice daily initiated 4 hours post-inoculation or 1,000 mg/kg twice daily initiated 12 hours post inoculation with SARS-CoV-2 MA10 resulted in reduction of lung viral titres and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals.

*Antiviral resistance*
Because nirmatrelvir is coadministered with low dose ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Pharmacodynamic effects

*Cardiac electrophysiology*
No clinically relevant effect of nirmatrelvir on QTcF interval was observed in a double-blind, randomised, placebo-controlled, cross-over study in 10 healthy adults. The model predicted upper bound of 90% confidence interval (CI) for baseline and ritonavir adjusted QTcF estimate was 1.96 ms at approximately 4-fold higher concentration than the mean steady-state peak concentration after a therapeutic dose of nirmatrelvir/ritonavir 300 mg/100 mg.

Clinical efficacy and safety

The efficacy of Paxlovid is based on the analysis of EPIC-HR, a Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised symptomatic adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible participants were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically related technological dependence, or were 60 years of age and older regardless of comorbidities. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study.

Participants were randomised (1:1) to receive Paxlovid (nirmatrelvir 300 mg/ritonavir 100 mg) or placebo orally every 12 hours for 5 days. The study excluded individuals with a history of prior COVID-19 infection or vaccination. The primary efficacy endpoint is the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated participants with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment], the mITT1 analysis set (all treated participants with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated participants with onset of symptoms ≤5 days).

A total of 2,246 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 46 years; 51% were male; 72% were White, 5% were Black, 45% were Hispanic or Latino and 14% were Asian; 66% of participants had onset of symptoms ≤ 3 days from initiation of study treatment; 47% of participants were serological negative at baseline. The mean (SD) baseline viral load was 4.63 $\log_{10}$ copies/mL (2.87); 26% of participants had a baseline viral load of > 10^7 (units); 6.2% of participants either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses.

The baseline demographic and disease characteristics were balanced between the Paxlovid and placebo groups.

Table 4 provides results of the primary endpoint in the mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for Paxlovid compared to placebo was 88% (95% CI: 75%, 94%).

**Table 4: Efficacy results in non-hospitalized adults with COVID-19 dosed within 5 days of symptom onset who did not receive COVID-19 monoclonal antibody treatment at baseline (mITT1 analysis set)**

| | **TRADENAME** (N=1039) | **Placebo** (N=1046) |
|---|---|---|
| COVID-19 related hospitalization or death from any cause through Day 28 | | |
| n (%) | 8 (0.8%) | 66 (6.3%) |
| Reduction relative to placebo[a] [95% CI], % | -5.62 (-7.21, -4.03) | |
| All-cause mortality through Day 28, % | 0 | 12 (1.1%) |

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mITT1=A modified intent-to-treat analysis set that includes all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment and were treated ≤5 days after COVID-19 symptom onset. The determination of primary efficacy was based on a planned interim analysis of 774 participants in mITT population. The estimated risk reduction was -6.3% with a 95% CI of (-9.0%, -3.6%) and 2-sided p-value <0.0001.

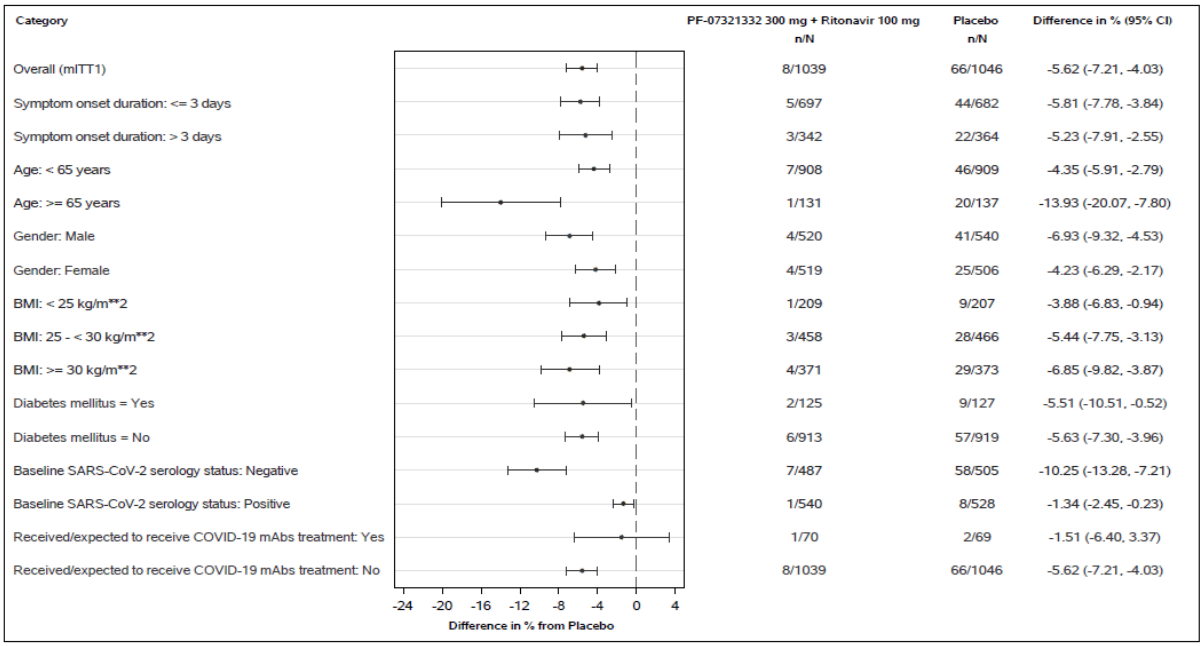
a. The estimated cumulative proportion of participants hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where participants without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

No deaths were reported in the Paxlovid group compared with 12 deaths in the placebo group. The proportions of participants who discontinued treatment due to an adverse event were 2.1% in the Paxlovid group and 4.2% in the placebo group.

Consistent results were observed in the mITT and mITT2 analysis populations. A total of 1379 participants were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the Paxlovid group, and 44/682 (6.45%) in the placebo group. The primary SARS-CoV-2 variant across both treatment arms was Delta (98.5%), including clades 21J, 21A, and 21I.

Similar trends have been observed across subgroups of participants (see Figure 1).

**Figure 1: Adults with COVID-19 dosed within 5 days of symptom onset with COVID-19-related hospitalization or death from any cause through Day 28**




Abbreviations: BMI=body mass index, COVID-19=Coronavirus Disease 2019, mITT1=A modified intent-to-treat analysis set that includes all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19

therapeutic monoclonal antibody treatment and were treated ≤5 days after COVID-19 symptom onset; N=number of participants in the category of the analysis set; SARS-COV-2=severe acute respiratory syndrome coronavirus 2.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti SARS-CoV-2 S or Elecsys SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on Normal approximation of the data are presented.

Relative to placebo, Paxlovid treatment was associated with an approximately 0.9 $log_{10}$ copies/mL greater decline in viral RNA levels in nasopharyngeal samples through Day 5, with similar results observed in the mITT, mITT1, and mITT2 analysis populations.

This medicinal product has been authorised under a so-called 'emergency used authorization scheme' scheme. This means that further evidence on this medicinal product is awaited. The Agency will review new information on this medicinal product at least every year and this Product information will be updated as necessary.

**Pharmacokinetic properties**
The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy participants.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations of nirmatrelvir. In healthy participants in the fasted state, the mean half-life ($t_{1/2}$) of a single dose of 150 mg nirmatrelvir administered alone was approximately 2 hours compared to 7 hours after administration of a single dose of 250 mg/100 mg nirmatrelvir /ritonavir thereby supporting a twice-daily administration regimen.

Upon administration of single dose of nirmatrelvir/ritonavir 250 mg/100 mg to healthy participants in the fasted state, the geometric mean (CV%) maximum concentration ($C_{max}$) and area under the plasma concentration-time curve from 0 to the time of last measurement ($AUC_{last}$) was 2.88 ug/mL (25%) and 27.6 ug*hr/mL (13%), respectively. Upon repeat-dose of nirmatrelvir/ritonavir 75 mg/100 mg, 250 mg/100 mg, and 500 mg/100 mg administered twice daily, the increase in systemic exposure at steady-state appears to be less than dose proportional. Multiple dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 were similar to Day 10 across all doses.

Absorption

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean nirmatrelvir (CV%) $C_{max}$ and area under the plasma concentration-time curve from 0 to infinity ($AUC_{inf}$) at steady-state was 2.21 µg/mL (33) and 23.01 µg*hr/mL (23), respectively. The median (range) time to $C_{max}$ ($T_{max}$) was 3.00 hrs (1.02-6.00). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (1.8) hours.

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV%) $C_{max}$ and $AUC_{inf}$ was 0.36 µg/mL (46) and 3.60 µg*hr/mL (47), respectively. The median (range) time to $C_{max}$ ($T_{max}$) was 3.98 hrs (1.48-4.20). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (2.2) hours.

*Effect of food on oral absorption*
Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean $C_{max}$ and 1.6% increase in mean $AUC_{last}$) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir coadministered with ritonavir tablets.

Distribution

The protein binding of nirmatrelvir in human plasma is approximately 69%.

The protein binding of ritonavir in human plasma is approximately 98-99%.

Biotransformation

*In vitro* studies assessing nirmatrelvir without concomitant ritonavir suggest that nirmatrelvir is primarily metabolised by CYP3A4. Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 *in vitro* at clinically relevant concentrations. *In vitro* study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8, and CYP2C9. The clinical relevance is unknown. Based on in vitro data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations. Administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In plasma, the only drug-related entity observed was unchanged nirmatrelvir. Minor oxidative metabolites were observed in the faeces and urine.

*In vitro* studies utilising human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of oxidation metabolite M–2.

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolised by CYP3A4) and other protease inhibitors may influence the pharmacokinetics of ritonavir.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Ritonavir also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

Elimination

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact drug. Approximately 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and faeces, respectively. N irmatrelvir was the predominant drug-related entity with small amounts of metabolites arising from hydrolysis reactions in excreta. In plasma, the only drug-related entity quantifiable was unchanged nirmatrelvir.

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir.

Specific populations

The pharmacokinetics of nirmatrelvir/ritonavir based on age and gender have not been evaluated.

*Racial or ethnic groups*
Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants.

*Patients with renal impairment*

Compared to healthy controls with no renal impairment, the $C_{max}$ and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

*Patients with hepatic impairment*
Compared to healthy controls with no hepatic impairment, the pharmacokinetics of nirmatrelvir in subjects with moderate hepatic impairment was not significantly different. Adjusted geometric mean ratio (90% CI) of $AUC_{inf}$ and $C_{max}$ of nirmatrelvir comparing moderate hepatic impairment (test) to normal hepatic function (reference) were 98.78% (70.65%, 138.12%) and 101.96% (74.20%, 140.11%), respectively.

Interaction studies conducted with nirmatrelvir/ritonavir

CYP3A4 was the major contributor to the oxidative metabolism of nirmatrelvir, when nirmatrelvir was tested alone in human liver microsomes. Ritonavir is an inhibitor of CYP3A and increases plasma concentrations of nirmatrelvir and other drugs that are primarily metabolised by CYP3A. Despite being coadministered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of nirmatrelvir.

The effects of coadministration of Paxlovid with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and $C_{max}$ are summarised in Table 5 (effect of other medicinal products on nirmatrelvir).

**Table 5: Interactions with other medicinal products: pharmacokinetic parameters for nirmatrelvir in the presence of the coadministered medicinal products**

| Coadministered medicinal product | Dose (schedule) | | N | Ratio (in combination with coadministered medicinal product/alone) of nirmatrelvir pharmacokinetic parameters (90% CI); no effect=100 | |
|---|---|---|---|---|---|
| | Coadministered medicinal product | nirmatrelvir / ritonavir | | $C_{max}$ | AUC[a] |
| carbamazepine[b] | 300 mg twice daily (16 doses) | 300 mg/100 mg twice daily (5 doses) | 9 | 56.82 (47.04, 68.62) | 44.50 (33.77, 58.65) |
| itraconazole | 200 mg once daily (8 doses) | 300 mg/100 mg twice daily (5 doses) | 11 | 118.57 (112.50, 124.97) | 138.82 (129.25, 149.11) |

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; $C_{max}$=maximum plasma concentrations.
a. For carbamazepine, AUC=$AUC_{inf}$, for itraconazole, AUC=$AUC_{tau}$.
b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

The effects of co-administration of Paxlovid with oral midazolam (CYP3A4 substrate) or dabigatran (P-gp substrate) on the midazolam and dabigatran AUC and $C_{max}$, respectively, are summarized in Table 6.

**Table 6: Effect of nirmatrelvir/ritonavir on pharmacokinetics of coadministered drug**

| Coadministered medicinal product | Dose (schedule) | | N | Percent ratio[a] of test/reference of geometric means (90% CI); no effect=100 | |
|---|---|---|---|---|---|
| | Coadministered medicinal product | nirmatrelvir/ ritonavir | | $C_{max}$ | AUC[b] |
| midazolam[c] (oral) | 2 mg (1 dose) | 300 mg/100 mg twice daily (9 doses)[b] | 10 | 368.33 (318.91, 425.41) | 1430.02 (1204.54, 1697.71) |
| dabigatran[c] | 75 mg (1 dose) | 300 mg/100 mg twice daily (5 doses)[b] | 24 | 233.06 (172.14, 315.54) | 194.47 (155.29, 243.55) |

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; $C_{max}$=maximum plasma concentrations.

a. Percent ratio of test (i.e., midazolam or dabigatran in combination with nirmatrelvir/ritonavir)/reference (i.e., midazolam or dabigatran alone).
b. AUC=$AUC_{inf}$ for both midazolam and dabigatran.
c. For midazolam, Test=nirmatrelvir/ritonavir plus midazolam, Reference=midazolam. Midazolam is an index substrate for CYP3A4. For dabigatran, Test=nirmatrelvir/ritonavir plus dabigatran, Reference=dabigatran. Dabigatran is an index substrate for P-gp.

**Preclinical safety data**

Toxicology

Repeat-dose toxicity studies up to 1 month duration of nirmatrelvir in rats and monkeys resulted in no adverse findings.

Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Carcinogenesis

Paxlovid has not been evaluated for the potential to cause carcinogenicity.

Nirmatrelvir has not been evaluated for the potential to cause carcinogenicity.

Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumorigenic potential specific for these species, but are regarded as of no relevance for humans.

Mutagenesis

Paxlovid has not been evaluated for the potential to cause mutagenicity.

Nirmatrelvir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human lymphoblastoid TK6 cells and *in vivo* rat micronucleus assays.

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Reproductive toxicity

*NIRMATRELVIR*
In a fertility and early embryonic development study, nirmatrelvir was administered to male and female rats by oral gavage at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days prior to mating, throughout the mating phase, and continued through Gestation Day (GD) 6 for females and for a total of 32 doses for males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day representing 12x/4.3x based on the predicted human $C_{max}/AUC_{24}$ at a twice-daily dose of 300 mg/100 mg nirmatrelvir/ritonavir.

The potential embryo-foetal toxicity of nirmatrelvir was evaluated in the definitive rat and rabbit studies at doses up to 1,000 mg/kg/day. There was no nirmatrelvir-related effect in any of the parameters in the rat embryo-foetal development (EFD) study up to the highest dose of 1,000 mg/kg/day (exposure margin of 16x/7.8x based on total $C_{max}/AUC_{24}$ over the predicted human exposures at a dose of 300 mg/100 mg nirmatrelvir/ritonavir twice daily). In the rabbit EFD study, there was no nirmatrelvir-related effect on foetal morphology or embryo-foetal viability up to the highest dose of 1,000 mg/kg/day (exposure margin of 24x/10x based on total $C_{max}/AUC_{24}$), however adverse nirmatrelvir-related lower foetal body weights (0.91x control) were observed at 1,000 mg/kg/day in the presence of nonadverse, low magnitude effects on maternal body weight change and food consumption at this dose. Growth delay is likely reversible following cessation of exposure in human, and it was not present at the intermediate dose (10x/2.8x $C_{max}/AUC_{24}$ over the predicted clinical exposure). There were no nirmatrelvir-related severe manifestations of developmental toxicity (malformations and embryo-foetal lethality) at the highest dose tested, 1,000 mg/kg/day.

*Ritonavir*
Ritonavir produced no effects on fertility in rats.

Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits. Increased incidences of early resorptions, ossification delays and developmental variations, as well as decreased foetal body weights were observed in the rat in the presence of maternal toxicity. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose). In the rabbit, resorptions, decreased litter size and decreased foetal weights were observed in the presence of maternal toxicity. In pre- and post-natal development study in rats, administration 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through Post-natal Day 20 resulted in no developmental toxicity.

## OVERDOSE

Treatment of overdose with Paxlovid should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Paxlovid.

## INCOMPATIBILITIES

Not applicable.

## SHELF-LIFE

24 months for Freiburg/Freiburg
18 months for Freiburg/Ascoli

## SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C.
Do not refrigerate or freeze.

## NATURE AND CONTENTS OF CONTAINER

Paxlovid is packaged in cartons containing 5 daily-dose OPA/Al/PVC foil blister cards of 30 tablets. Each daily blister card contains 4 nirmatrelvir tablets and 2 ritonavir tablets.

## INSTRUCTIONS FOR HEALTH CARE PROVIDERS

As the health care provider, you must communicate to your patient or parent/caregiver information consistent with the "**Informasi Produk untuk Pasien** (Fact Sheet for patient and Parents/Caregivers)" including:
1. That the Badan POM has authorized emergency use of Paxlovid.
2. The potential consequences of refusing Paxlovid.
3. The significant known and potential risks and benefits of Paxlovid, as supplied under this EUA.
4. The alternative products that are available and their benefits and risks, including clinical trials.

## MANDATORY REQUIREMENTS FOR PAXOLOVID ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this product under EUA and to optimize the potential benefit of Paxlovid, the following items are required. Use of Paxlovid under this EUA is limited to the following (all requirements must be met):

1. Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

2. As the health care provider, you must communicate to your patient or parent/caregiver information consistent with the "**Informasi Produk untuk Pasien**" prior to the patient receiving Paxlovid. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:

a) Given the "**Informasi Produk untuk Pasien**",
b) Informed of alternatives to receiving Paxlovid, and

c) Informed that Paxlovid is an unapproved drug that is authorized for use under Emergency Use Authorization.

3. Paxlovid is contraindicated in patients:
- with a history of clinically significant hypersensitivity to the active substances (nirmatrelvir/ritonavir) or to any of the excipients listed in section **COMPOSITION**.
- with severe hepatic impairment.
- with severe renal impairment.

Paxlovid is also contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. Paxlovid is also contraindicated with medicinal products that are potent CYP3A inducers where significantly reduced plasma nirmatrelvir/ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance.

4. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory responses to requests from Badan POM for information about adverse events and medication errors following receipt of Paxlovid.

5. The prescribing health care provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and adverse events (death, serious adverse events*) considered to be potentially related to Paxlovid occurring during Paxlovid treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words **"Paxlovid under Emergency Use Authorization (EUA)"** in the description section of the report.

• Submit adverse event reports to:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

• Submitted reports should include in the field name, "Describe Event, Problem, Use/Medication Error" the statement "**Paxlovid Treatment under EUA**"

*Serious Adverse Events are defined as:
• death;
• a life-threatening adverse event;
• inpatient hospitalization or prolongation of existing hospitalization;
• a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
• a congenital anomaly/birth defect;
• a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

## APPROVED AVAILABLE ALTERNATIVES

There is no approved available alternative product. There are EUAs for other COVID-19 treatments. The health care provider should visit https://clinicaltrials.gov/ and https://trialsearch.who.int/ to determine whether the patient may be eligible for enrollment in a clinical trial.

## AUTHORITY FOR ISSUANCE OF THE EUA

Indonesian Government has declared an emergency situation as a result of pandemic outbreak of COVID-19 that justifies the emergency need of using Paxlovid as an option in this situation. In response to that situation, the Badan POM has issued an Emergency Use Authorization (EUA) for the use of Paxlovid for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

As a health care provider, you must comply with the mandatory requirements of the EUA listed above.

Although limited scientific information is available, it is reasonable to believe that Paxlovid is effective for treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19, as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency. Serious adverse events related to the use of Paxlovid must be reported to Badan POM through Pusat Farmakovigilans/MESO Nasional, Badan Pengawas Obat dan Makanan online http://e-meso.pom.go.id/ADR. Please include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the following statement: **Paxlovid Treatment under EUA**.

This EUA for Paxlovid will end when the Badan POM determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

## PHARMACEUTICAL FORM

Nirmatrelvir
Film-coated tablet (tablet).
Pink, oval, with a dimension of approximately 17.6 mm in length and 8.6 mm in width debossed with 'PFE' on one side and '3CL' on the other side.

Ritonavir
Film-coated tablet (tablet).
White to off white, capsule shaped tablets, with a dimension of approximately 17.1 mm in length and 9.1 mm in width, debossed with 'H' on one side and 'R9' on other side.

## PRESENTATION

| Product | EUA No. | Manufacturer Nirmatrelvir Film-coated tablet/Ritonavir Film-coated tablet | Packager/Releaser | Shelf life |
|---|---|---|---|---|
| **PAXLOVID** Box of 5 blisters @ 4 Nirmatrelvir 150 mg Film-coated Tablets and 2 Ritonavir 100 mg Film-coated Tablets. | EUA2258501817A1 | Pfizer Freiburg/Hetero | Pfizer Freiburg | 24 months |
| | EUA2254201117A1 | Pfizer Freiburg/Hetero | Pfizer Ascoli | 18 months |

**HARUS DENGAN RESEP DOKTER**

**Nirmatrelvir Film-coated Tablet, manufactured by:**
Pfizer Manufacturing Deutschland GmbH
Freiburg, Germany

**Ritonavir Film-coated Tablet, manufactured by:**
Hetero Labs Limited
Hyderabad, India

**Packed and released by:**
- Pfizer Manufacturing Deutschland GmbH
  Freiburg, Germany
- Pfizer Italia S.r.l.
  Ascoli Piceno, Italy

**Imported by:**
PT. Pfizer Indonesia
Jakarta, Indonesia

**DATE OF REVISION OF THE TEXT**

04/2023