1. NAME OF THE MEDICINAL PRODUCT

Paxlovid®

Nirmatrelvir 150 mg film-coated tablets and ritonavir 100 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nirmatrelvir

Film-coated 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.
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.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 (see section 5.1).

4.2 Posology and method of 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.

Posology

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 every 12 hours 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 even if baseline COVID-19 symptoms are mild.

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 hospitalisation 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 dosage adjustment is currently recommended for elderly patients.

Renal impairment
No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min).

In patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min), the dosage 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 (see section 6.6).

Paxlovid is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min) or with renal failure as the appropriate dose has not yet been determined (see sections 4.3 and 5.2).

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 (Child-Pugh Class C) hepatic impairment, therefore, Paxlovid is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

Concomitant therapy with ritonavir- or cobicistat-containing regimen
No dosage 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.

Method of administration

For oral use.

Paxlovid can be taken with or without food (see section 5.2). The tablets should be swallowed whole and not chewed, broken or crushed.

4.3 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 section 6.1.
- 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. Medicinal products listed in Table 1 and Table 2 (see section 4.5) are a guide and not considered a comprehensive list of all possible medicinal products that may be contraindicated with Paxlovid.

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.
Antianginal	ranolazine	Potentially increased plasma concentrations of ranolazine may result in serious and/or life-threatening reactions.
Anticancer agents	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 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	Increased plasma concentrations of lurasidone and pimozide result in serious and/or life-threatening reactions.
	quetiapine	Increased plasma concentrations of quetiapine may lead to coma.
Benign prostatic hyperplasia agents	silodosin	Increased plasma concentrations of benign prostatic hyperplasia agent.
Cardiovascular agents	eplerenone, ivabradine	Increased plasma concentrations of cardiovascular agents.

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

Medicinal product class	Medicinal products within class	Clinical comments
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischemia.
GI motility agent	cisapride	Increased plasma concentrations of cisapride, thereby increasing the risk of serious arrhythmias from this agent.
Immunosuppressants	voclosporin	Increased plasma concentrations of immunosuppressant.
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.
Migraine medications	eletriptan, ubrogepant	Increased plasma concentrations of migraine medications.
Mineralocorticoid receptor antagonists	finerenone	Increased plasma concentrations of mineralocorticoid receptor antagonist.
Opioid antagonists	naloxegol	Increased plasma concentrations of opioid antagonist.
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	triazolam, oral midazolam[a]	Increased plasma concentrations of triazolam and oral midazolam can increase risk of extreme sedation and respiratory depression.
Serotonin receptor 1A agonists/serotonin receptor 2A antagonists	flibanserin	Increased plasma concentrations of serotonin receptor 1A agonist/serotonin receptor 2A antagonist.
Vasopressin receptor antagonists	tolvaptan	Increased plasma concentrations of vasopressin receptor antagonist.
Interactions that result in decreased concentrations of nirmatrelvir/ritonavir as the concomitant medicinal products induce Paxlovid's CYP3A4 metabolic pathway		
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin, primidone,	Decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.
Anticancer agents	enzalutamide	Decreased plasma concentrations of nirmatrelvir/ritonavir may lead to 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
Antimycobacterials	rifampicin, rifapentine	Potentially decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	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 section 5.2, Interaction studies conducted with nirmatrelvir/ritonavir.

4.4 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.

Severe, life-threatening, and fatal adverse reactions due to drug interactions have been reported in patients treated with Paxlovid.

See Table 1 for medicinal products that are contraindicated for concomitant use with nirmatrelvir/ritonavir (see section 4.3) and Table 2 for potentially significant interactions with other medicinal products (see section 4.5). 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.

Coadministration of Paxlovid with calcineurin inhibitors and mTOR inhibitors
Consultation of a multidisciplinary group (e.g., involving physicians, specialists in immunosuppressive therapy, and/or specialists in clinical pharmacology) is required to handle the complexity of this coadministration by closely and regularly monitoring immunosuppressant blood concentrations and adjusting the dose of the immunosuppressant in accordance with the latest guidelines (see section 4.5).

Hypersensitivity reactions

Anaphylaxis, hypersensitivity reactions, and serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported with Paxlovid (see section 4.8). If signs and

symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Paxlovid (nirmatrelvir/ritonavir) is a strong inhibitor of CYP3A and an inhibitor of CYP2D6, P-gp and OATP1B1. Coadministration of Paxlovid with medicinal products that are primarily metabolised by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such medicinal products and increase the risk of adverse reactions.

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 Paxlovid 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, section 4.3).

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 (see section 4.3) 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**
$Alpha_1$-Adrenoreceptor antagonist	↑Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see section 4.3).
	↑Tamsulosin	Avoid concomitant use with Paxlovid.
Amphetamine derivatives	↑Methylphenidate, ↑Dexamphetamine	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.
Analgesic	↑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.
	↑Fentanyl ↑Hydrocodone ↑Oxycodone ↑Meperidine	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of these medicines. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl hydrocodone, oxycodone, or meperidine is concomitantly administered with Paxlovid. If concomitant use with Paxlovid is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information.

	↓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 section 4.3).
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 section 4.3).
	↑Digoxin	This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer.
	↑Disopyramide	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmic if available.
Antiasthmatic	↓Theophylline (43%, 32%)	An increased dose of theophylline may be required when coadministered with ritonavir, due to induction of CYP1A2.
Anticancer agents	Enzalutamide ↑Afatinib	Coadministration contraindicated due to potential loss of virologic response and possible resistance (see section 4.3). 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 C_{max} depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with Paxlovid (refer to the afatinib

		Product Label). 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 Label for dose 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 not recommended.
	↑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 Label 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.
	↑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 Label 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 section 4.3).

	↑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 section 4.3 and refer to the venetoclax Product Label). 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 Label for dosing instructions).
Anticoagulants	↑Apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for coadministration of apixaban with Paxlovid depend on the apixaban dose. Refer to the apixaban product label for more information.
	↑Dabigatran[a] (194%, 233%)	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran product label for further information.
	↑Rivaroxaban (153%, 53%)	Inhibition of CYP3A and P-gp lead to increased plasma levels and 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 Label).
	Warfarin, ↑↓S-Warfarin (9%, 9%), ↓↔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 section 4.3).
	Phenobarbital, Phenytoin, Primidone	Coadministration contraindicated due to potential loss of virologic response and possible resistance (see section 4.3).
	↓Divalproex, ↓Lamotrigine	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.
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.
	↑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.
Antifungals	↑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]	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when itraconazole is coadministered with ritonavir.
	↓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.
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 section 4.3).
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-HIV protease inhibitors	↑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 Label 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 Label for darunavir.

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 Label for maraviroc.
	↓Zidovudine (25%, ND)	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.
Anti-infectives	↓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.
	↑Clarithromycin (77%, 31%), ↓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 creatine clearance of 30 to 60 ml/min the dose should be reduced by 50%, Paxlovid is contraindicated in patient with severe renal impairment (see sections 4.2 and 4.3).
	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 period is recommended (see section 4.4 and refer to the delamanid product label).
	↑Erythromycin	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is coadministered with ritonavir.
	↑Fusidic acid	Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).
	Sulfamethoxazole/Trimethoprim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
Antimycobacterial	↑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 (refer to the bedaquiline product label).
	↑Rifabutin (4-fold, 2.5-fold) ↑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, Rifapentine	Rifampicin and rifapentine are strong CYP3A4 inducers, and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. Concomitant use of rifampicin and rifapentine with Paxlovid is contraindicated (see section 4.3).

Antiparasitic agent	↓Albendazole	Significant decreases in plasma concentrations of albendazole and its active metabolite may occur due to induction by ritonavir, with a risk of decreased albendazole efficacy. Clinical monitoring of therapeutic response and possible adjustment of albendazole dosage during treatment with Paxlovid and following discontinuation is recommended.
Antipsychotics	↑Lurasidone, ↑Pimozide	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone and pimozide are expected to increase. The concomitant administration with lurasidone and pimozide is contraindicated (see section 4.3).
	↑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 section 4.3).
	↑Clozapine	If coadministration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
	↑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.
Benign prostatic hyperplasia agents	↑Silodosin	Coadministration contraindicated due to potential for postural hypotension (see section 4.3).
Calcium channel antagonist	↑Amlodipine, ↑Diltiazem, ↑Nifedipine, ↑Verapamil	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.

Cardiovascular agents	↑Eplerenone	Coadministration with eplerenone is contraindicated due to potential for hyperkalaemia (see section 4.3).
	↑Ivabradine	Coadministration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances (see section 4.3).
	↑Aliskiren, ↑Ticagrelor, ↑Vorapaxar	Avoid concomitant use with Paxlovid.
	↓Clopidogrel	Coadministration is likely to result in decreased plasma concentrations of the active metabolite of clopidogrel.
	↑Cilostazol	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol Product Label for more information.
	↑Mavacamten	Coadministration with mavacamten may increase mavacamten plasma concentration and increase the risk of heart failure. Discontinue mavacamten for the duration of Paxlovid treatment. Resumption of mavacamten within 5 days of completing Paxlovid may result in higher exposure of mavacamten. Refer to the mavacamten Product Label for more information.
Corticosteroids primarily metabolized by CYP3A	↑Betamethasone, ↑Budesonide, ↑Ciclesonide, ↑Fluticasone, ↑Methylprednisolone, ↑Mometasone, ↑Triamcinolone	Coadministration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. Alternative corticosteroids including beclomethasone and prednisone should be considered.
	↑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.
Corticosteroids	↑Prednisolone (28%, 9%)	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.
Cystic fibrosis transmembrane conductance regulator potentiators	Lumacaftor/Ivacaftor	Coadministration contraindicated due to potential loss of virologic response and possible resistance (see section 4.3).
	↑Ivacaftor, ↑Elexacaftor/ Tezacaftor/Ivacaftor, ↑Tezacaftor/Ivacaftor	Reduce dosage when coadministered with Paxlovid. Refer to the individual product label for more information.
Dipeptidyl peptidase 4 (DPP4) inhibitors	↑Saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label for more information.
Endothelin Antagonists	↑Bosentan	Coadministration of bosentan and ritonavir may increase steady-state bosentan C_{max} and AUC.
Ergot Derivatives	↑Dihydroergotamine, ↑Ergonovine, ↑Ergotamine, ↑Methylergonovine	Ritonavir coadministration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 4.3)
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 to be avoided due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
Herbal products	St. John's Wort (*Hypericum perforatum*)	Coadministration contraindicated due to potential loss of virologic response and possible resistance (see section 4.3).
HMG-CoA reductase inhibitors	↑Lovastatin, ↑Simvastatin	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 section 4.3).

		Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of Paxlovid, during the 5 days of Paxlovid treatment and for 5 days after completing Paxlovid.
	↑Atorvastatin, ↑Rosuvastatin[a]	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with Paxlovid. Atorvastatin and rosuvastatin do not need to be held prior to or after completing Paxlovid
	↑Fluvastatin, ↑Pravastatin,	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.
Hormonal Contraceptive	↓Ethinyl estradiol (40%, 32%)	Due to reductions in ethinylestradiol concentrations, barrier or other non-hormonal methods of contraception should be considered during the 5 days of Paxlovid treatment and until one menstrual cycle after stopping Paxlovid. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives.
Immunosuppressants	↑Voclosporin	Coadministration contraindicated due to potential for acute and/or chronic nephrotoxicity (see section 4.3).
	Calcineurin inhibitors: ↑Cyclosporine ↑Tacrolimus	Avoid concomitant use of calcineurin inhibitors and mTOR inhibitors during treatment with Paxlovid.
	mTOR inhibitors: ↑Everolimus, ↑Sirolimus	Dose adjustment of the immunosuppressant and close and regular monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions are recommended during and after treatment with Paxlovid. Refer to the individual immunosuppressant product label and latest guidelines for further information and obtain expert consultation of a multidisciplinary group (see section 4.4).

Janus kinase (JAK) inhibitors	↑Tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information.
	↑Upadacitinib	Dosing recommendations for coadministration of upadacitinib with Paxlovid depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.
Long-acting beta-adrenoceptor agonists	↑Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected. Therefore, avoid concomitant use with Paxlovid.
Microsomal triglyceride transfer protein (MTTP) inhibitor	↑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 due to potential for hepatotoxicity and gastrointestinal adverse reactions (refer to the lomitapide product label) (see section 4.3).
Migraine medications	↑Eletriptan	Coadministration of eletriptan within at least 72 hours of Paxlovid is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events (see section 4.3).
	↑Ubrogepant	Coadministration of ubrogepant with Paxlovid is contraindicated due to potential for serious adverse reactions (see section 4.3).
	↑Rimegepant	Avoid concomitant use with Paxlovid.
Mineralocorticoid receptor antagonists	↑Finerenone	Coadministration contraindicated due to potential for serious adverse reactions including hyperkalaemia, hypotension, and hyponatremia (see section 4.3).
Muscarinic receptor antagonists	↑Darifenacin	The darifenacin daily dose should not exceed 7.5 mg when coadministered with Paxlovid. Refer to the darifenacin product label for more information.
Neuropsychiatric agents	↑Suvorexant	Avoid concomitant use of suvorexant with Paxlovid.

	↑Aripiprazole, ↑Brexpiprazole, ↑Cariprazine, ↑Iloperidone, ↑Lumateperone, ↑Pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to the individual product label for more information.
Opioid antagonists	↑Naloxegol	Coadministration contraindicated due to the potential for opioid withdrawal symptoms (see section 4.3).
PDE5 Inhibitors (Erectile dysfunction agents)	↑Avanafil (13-fold, 2.4-fold)	Concomitant use of avanafil with Paxlovid is contraindicated (see section 4.3) because a safe and effective avanafil dosage regimen has not been established.
	↑Sildenafil (11-fold, 4-fold), ↑Tadalafil (124%, ↔)	Dosage adjustment is recommended for use of sildenafil or tadalafil with Paxlovid. Concomitant use of sildenafil or tadalafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be made with caution and with increased monitoring for adverse reactions. Sildenafil doses should not exceed 25 mg in 48 hours and tadalafil doses should be reduced to no more than 10 mg every 72 hours. Refer to individual product label for more information.
	↑Vardenafil (49-fold, 13-fold)	Concomitant use of vardenafil with Paxlovid is contraindicated (see section 4.3).
PDE5 inhibitors (Pulmonary hypertension agents)	↑Sildenafil (Revatio®)	Coadministration of sildenafil with Paxlovid is contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope (see section 4.3).
	↑Tadalafil (Adcirca®)	Avoid concomitant use of tadalafil with Paxlovid.
sGC stimulators (Pulmonary hypertension agents)	↑Riociguat	Dosage adjustment is recommended for riociguat. Refer to the riociguat product label for more information.
Sedatives/hypnotics	↑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 section 4.3), 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 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 section 4.3).
	↑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, ↑Clonazepam, ↑Clorazepate, ↑Diazepam, ↑Estazolam, ↑Flurazepam	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, clonazepam, clorazepate, diazepam, estazolam, and flurazepam. A dose decrease may be needed for these medicinal products when coadministered with Paxlovid and careful monitoring of therapeutic and adverse effects is recommended when concomitantly administered with Paxlovid.

	↑Zolpidem (28%, 22%)	Zolpidem and ritonavir may be coadministered with careful monitoring for excessive sedative effects.
Serotonin receptor 1A agonists/ serotonin receptor 2A antagonists	↑Flibanserin	Coadministration contraindicated due to potential for hypotension, syncope, and CNS depression (see section 4.3).
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 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.
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.
Vasopressin receptor antagonists	↑Tolvaptan	Coadministration contraindicated due to potential for dehydration, hypovolemia and hyperkalaemia (see section 4.3).

Abbreviations: ALT=alanine aminotransferase, AUC= area under the curve; C_{max}= maximum concentrations.
a. See section 5.2, Interaction studies conducted with nirmatrelvir/ritonavir.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

There are limited 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.

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 section 4.5).

Pregnancy

There are limited data from the use of Paxlovid in pregnant women. Paxlovid should be used during pregnancy only if the potential benefits outweigh the potential risks for the mother and the foetus.

Animal data with nirmatrelvir have shown developmental toxicity in the rabbit (lower foetal body weights) but not in the rat. 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. There were no nirmatrelvir-related adverse effects in a pre- and postnatal developmental study in rats (see section 5.3).

A large number (6100 live births) of pregnant women were exposed to ritonavir during pregnancy; of these, 2800 live births were exposed during the first trimester. 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 section 5.3).

Breast-feeding

In a clinical pharmacokinetics study, 8 healthy lactating women who were at least 12 weeks postpartum were administered 3 doses (steady-state dosing) of 300 mg/100 mg nirmatrelvir/ritonavir. Nirmatrelvir and ritonavir were excreted in breastmilk in small amounts, with a milk to plasma AUC ratio of 0.26 and 0.07, respectively. The mean (range) estimated daily infant dose (assuming average milk consumption of 150 mL/kg/day), was 1.8% (1.3-2.5%) and 0.2% (0.1-0.3%) of the maternal dose.

There are no available data on the effects of nirmatrelvir or ritonavir on the breast-fed newborn/infant or on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Paxlovid and for 48 hours 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 section 5.3).

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

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

The safety of Paxlovid was based on data from three phase 2/3 randomised, placebo-controlled trials in non-hospitalised adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection (see section 5.1):

- Study C4671005 (EPIC-HR) and Study C4671002 (EPIC-SR) investigated Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) every 12 hours for 5 days in symptomatic participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Participants were to present with mild to moderate COVID-19 at baseline.
- Study C4671006 (EPIC-PEP) investigated Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) every 12 hours for 5 or 10 days in asymptomatic household contact of individuals with a recent diagnosis of SARS-CoV-2 infection. Participants were to have a negative SARS-CoV-2 result at baseline.

Across the three studies, 3,515 participants received a dose of Paxlovid and 2,585 participants received a dose of placebo. The most common adverse reactions (≥ 1% incidence in the Paxlovid group and occurring at a greater frequency than in the placebo group) were dysgeusia (5.9% and 0.4%, respectively) and diarrhoea (2.9% and 1.9%, respectively).

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	Uncommon	Hypersensitivity*
	Rare	Anaphylaxis*
Nervous system disorders	Common	Dysgeusia, Headache
Vascular disorders	Uncommon	Hypertension*
Gastrointestinal disorders	Common	Diarrhoea, Nausea*
	Uncommon	Vomiting, Abdominal pain*
Skin and subcutaneous tissue disorders	Rare	Toxic epidermal necrolysis* Stevens-Johnson syndrome*
General disorders and administration site conditions	Rare	Malaise*

* Adverse drug reaction (ADR) identified post-marketing.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code: J05AE30.

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nsp5 protease. Inhibition of the SARS-CoV-2 M^{pro} renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication.

Ritonavir is not active against SARS-CoV-2 M^{pro}. 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 differentiated normal human bronchial epithelial (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 exposure.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7 (P252L+F294L), BF.7 (T243I), BQ.1.11, BQ.1, XBB.1.5, EG.5 and JN.1 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 88 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes $\leq$1.8 relative to the USA-WA1/2020 isolate.

In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes $\leq$1.1 relative to USA-WA1/2020.

Antiviral resistance in cell culture and biochemical assays

SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 4 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 4: SARS-CoV-2 M^{pro} amino acid substitutions selected by nirmatrelvir in cell culture

Single substitution (EC_{50} value fold change)	T21I (1.1-4.8), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (1.4-5.5).
$\geq$2 substitutions (EC_{50} value fold change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1-8.9), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

Abbreviations: ND=no data (substitution emerged from nirmatrelvir resistance selection but has not been tested for EC_{50} determination in an antiviral assay).

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced activity (fold-change based on Ki values) of nirmatrelvir: Y54A (25), F140A (21), F140L (7.6), F140S (230), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35), E166G (6.2), E166V (7,700), P168del (9.3), H172Y (250), A173S (4.1), A173V (16), R188G (38), Q192L (29), Q192P (7.8), and V297A (3.0). In addition, the following combinations of M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity: T21I+S144A (20), T21I+E166V (11,000), T21I+A173V (15), L50F+E166V (4,500), E55L+S144A (56), T135I+T304I (5.1), F140L+A173V (95), S144A+T304I (28), E166V+L232R (5,700), P168del+A173V (170), H172Y+P252L (180), A173V+T304I (28), T21I+S144A+T304I (51), T21I+A173V+T304I (55), L50F+E166A+L167F (180), T21I+L50F+A193P+S301P (7.3), L50F+F140L+L167F+T304I (190), and T21I+C160F+A173V+V186A+T304I (28). The following substitutions and substitution combinations emerged in cell culture but conferred <3-fold reduced nirmatrelvir activity in biochemical assays: T21I (1.6), L50F (0.2), P108S (2.9), T135I (2.2), C160F (0.6), L167F (1.5), T169I (1.4), V186A (0.8), A191V (0.8), A193P (0.9), P252L (0.9), S301P (0.2), T304I (1.0), T21I+T304I (1.8), and L50F+T304I (1.3). The clinical significance of these substitutions is unknown.

Most single and some double M^{pro} amino acid substitutions identified which reduced the susceptibility of SARS-CoV-2 to nirmatrelvir resulted in an EC_{50} shift of <5-fold compared to wild type SARS-CoV-2 in an antiviral cell assay. Virus containing E166V shows the greatest reduction in susceptibility to nirmatrelvir and appears to have replication defect since it either could not be generated or had a very low virus titer. In general, triple and some double M^{pro} amino acid substitutions led to EC_{50} changes of > 5-fold to that of wild type. The clinical significance needs to be further understood, particularly in the context of nirmatrelvir high clinical exposure (≥5× EC_{90}). Thus far, these substitutions have not been identified as treatment-emergent substitutions associated with hospitalisation or death from the EPIC-HR or EPIC-SR studies.

Treatment-emergent substitutions were evaluated among participants in clinical trials EPIC-HR/SR with sequence data available at both baseline and a post-baseline visit (n=907 Paxlovid-treated participants, n=946 placebo-treated participants). SARS-CoV-2 M^{pro} amino acid changes were classified as Paxlovid treatment-emergent substitutions if they were absent at baseline, occurred at the same amino acid position in 3 or more Paxlovid-treated participants and were ≥2.5-fold more common in Paxlovid-treated participants than placebo-treated participants post-dose. The following Paxlovid treatment-emergent M^{pro} substitutions were observed: T98I/R/del (n=4), E166V (n=3), and W207L/R/del (n=4). Within the M^{pro} cleavage sites, the following Paxlovid treatment-emergent substitutions were observed: A5328S/V (n=7) and S6799A/P/Y (n=4). These cleavage site substitutions were not associated with the co-occurrence of any specific M^{pro} substitutions.

None of the treatment-emergent substitutions listed above in M^{pro} or M^{pro} cleavage sites occurred in Paxlovid-treated participants who experienced hospitalisation. Thus, the clinical significance of these substitutions is unknown.

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.

Viral load rebound

Post-treatment increases in SARS-CoV-2 nasal RNA levels (i.e., viral RNA rebound) were observed on Day 10 and/or Day 14 in a subset of Paxlovid and placebo recipients in EPIC-HR and EPIC-SR, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment nasal viral RNA rebound varied according to analysis parameters but was generally similar among Paxlovid and placebo recipients. A similar or smaller percentage of placebo recipients compared to Paxlovid recipients had nasal viral RNA results < lower limit of quantitation (LLOQ) at all study timepoints in both the treatment and post-treatment periods.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalisation or death from any cause through Day 28 following the single 5-day course of Paxlovid treatment. The clinical relevance of post-treatment increases in viral RNA following Paxlovid or placebo treatment is unknown.

EPIC-HR and EPIC-SR were not designed to evaluate symptomatic viral RNA rebound, and most episodes of symptom rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were routinely assessed). The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among Paxlovid and placebo recipients.

Cross-resistance

Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro} inhibitors).

Pharmacodynamic effects

Cardiac electrophysiology
At 3 times the steady-state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

Effects on viral RNA levels
Changes from baseline relative to placebo at Day 5 in viral RNA levels in nasopharyngeal samples are summarised by study in Table 5.

Table 5: Analysis of change from baseline to Day 5 in log_{10} (viral RNA levels, copies/mL); EPIC-HR, EPIC-SR, and EPIC-PEP (mITT1 analysis set)

	EPIC-HR (mITT1[a])		EPIC-SR (mITT1[b])		EPIC-PEP (mITT1[c])	
	Paxlovid	**Placebo**	**Paxlovid**	**Placebo**	**Paxlovid**	**Placebo**
Primary VoC[d]	Delta (99%)		Delta (79%) Omicron (19%)		Omicron (82%) Delta (18%)	
Baseline	n=764	n=784	n=542	n=514	n=86[e]	n=29
Median	6.075	5.990	6.615	6.430	4.330	4.930
Mean (SD)	5.780 (2.077)	5.617 (2.143)	6.214 (1.794)	6.045 (1.862)	4.647 (1.780)	4.837 (1.577)
Day 5	n=676	n=683	n=498	n=473	n=84	n=28
Median change from baseline	-2.990	-2.160	-3.680	-2.630	-3.020	-1.895
Median reduction relative to placebo	-0.830		-1.050		-1.125	
Adjusted change from baseline, mean (95% CI)	-3.087 (-3.219, -2.955)	-2.310 (-2.439, -2.180)	-3.419 (-3.584, -3.253)	-2.551 (-2.723, -2.378)	-3.279 (-3.795, -2.762)	-1.715 (-2.524, -0.906)
Mean reduction relative to placebo, mean (95% CI)	-0.777 (-0.937, -0.617)		-0.868 (-1.073, -0.663)		-1.564 (-2.418, -0.710)	
p-value	<0.0001		<0.0001		0.0004	

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT=modified intent-to-treat; RT-PCR=reverse transcriptase–polymerase chain reaction; SD=standard deviation; VoC=variant of concern.

a. 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.
b. All treated participants with at least 1 post-baseline visit through Day 28; 57% of these participants were vaccinated against COVID-19 at baseline.

c. All treated participants with a positive RT-PCR result at baseline.
d. VoC lineage percentage relates to the entire study populations for EPIC-HR and EPIC-SR, and to the COVID-19-infected participants in the mITT and mITT1 populations of EPIC-PEP.
e. Participants who received Paxlovid for 5 days and 10 days are combined.

The degree of reduction in viral RNA levels relative to placebo following 5 days of Paxlovid treatment was similar across studies, including those enrolling unvaccinated participants (EPIC-HR) and those enrolling both unvaccinated and vaccinated participants (EPIC-SR and EPIC-PEP).

Effect on lipids
The changes in lipids in nirmatrelvir/ritonavir treated group were not statistically different than placebo/ritonavir treated group in an exploratory analysis of lipids in multiple ascending dose cohorts in which healthy participants were randomised to receive either escalating doses (75, 250 and 500 mg) of nirmatrelvir (n=4 per cohort) or placebo (n=2 per cohort), enhanced with ritonavir 100 mg, twice a day for 10 days.

In participants receiving placebo/ritonavir twice a day, a modest increase in cholesterol (≤ 27.2 mg/dL), LDL cholesterol (≤ 23.2 mg/dL), triglycerides (≤ 64.3 mg/dL) and decrease in HDL cholesterol (≤ 4 mg/dL) was observed. The clinical significance of such changes with short-term treatment is unknown.

Clinical efficacy

Efficacy in participants at high risk of progressing to severe COVID-19 illness (EPIC-HR)
The efficacy of Paxlovid is based on the final 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. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study.

Participants were randomised (1:1) to receive Paxlovid (nirmatrelvir/ritonavir 300 mg/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 was the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28. Time to sustained alleviation and sustained resolution of all targeted symptoms through Day 28 were key secondary efficacy endpoints. These analyses were 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). Secondary efficacy endpoints included assessments of COVID-19 hospitalisation or death from any cause through Day 28 in the mITT1 analysis set.

A total of 2,113 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 45 years; 51% were male; 71% were White, 4% were Black or African American, 15% were Asian and 41% were Hispanic or Latino; 67% of participants had onset of symptoms ≤ 3 days before initiation of study treatment; 49% of participants were serological negative at baseline. The most frequently reported risk factors were BMI ≥ 25 kg/m^2 (1,692 [80.1%] participants), tobacco use (826 [39.1%] participants), hypertension (671 [31.8%] participants), age ≥ 60 years (438 [20.7%] participants), and diabetes mellitus (228 [10.8%] participants). Other risk factors were cardiovascular disorder (87 [4.1%] participants), chronic kidney disease (12 [0.6%] participants), chronic lung disease (100 [4.7%] participants), immunosuppression (13 [0.6%] participants), cancer (114 [0.5%] participants), neurodevelopmental disorders (3 [0.1%] participants), HIV infection (1 [<0.1%] participant) and device dependency (7 [0.3%] participants). The mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/mL (2.89); 27% of participants had a baseline viral load of ≥7 $\log_{10}$ copies/mL; 6% of participants either received or were expected to receive COVID-19 therapeutic mAb 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 6 provides results of the primary endpoint in the mITT1 analysis population demonstrating superiority of Paxlovid compared to placebo for COVID-19 related hospitalisation or death from any cause through Day 28. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for Paxlovid compared to placebo was 86% (95% CI: 72%, 93%). The determination of primary efficacy was based on a planned interim analysis of 754 participants in mITT population. The estimated risk reduction was -6.5% with a 95% CI of (-9.3%, -3.7%) and 2-sided p value <0.0001.

Table 6: Efficacy results in non-hospitalised adults with COVID-19 dosed within 5 days of symptom onset who did not receive COVID-19 mAb treatment at baseline (mITT1 analysis set)

	Paxlovid (N=977)	**Placebo (N=989)**
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%) Reduction relative to placebo[a] [95% CI], %	9 (0.9%) -5.64 (-7.31, -3.97)	64 (6.5%)
p-value	<0.0001	
All-cause mortality through Week 24, %	0	15 (1.5%)

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (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 mAb treatment and were treated ≤5 days after COVID-19 symptom onset).

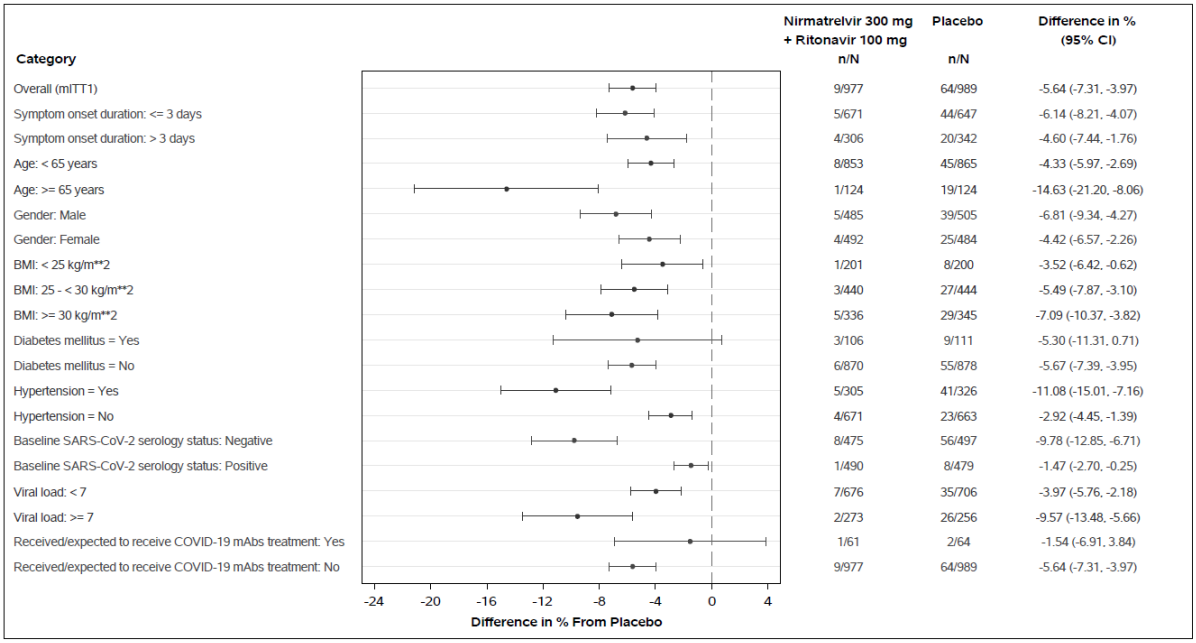
a. The estimated cumulative proportion of participants hospitalised or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where participants without hospitalisation and death status through Day 28 were censored at the time of study discontinuation.

Through Week 24, no deaths were reported in the Paxlovid group compared with 15 deaths in the placebo group. The proportions of participants who discontinued treatment due to an adverse event were 2.0% in the Paxlovid group and 4.3% in the placebo group.

Consistent results were observed in the final mITT and mITT2 analysis populations. A total of 1,318 subjects were included in the mITT analysis population. The event rates were 5/671 (0.75%) in the Paxlovid group, and 44/647 (6.80%) in the placebo group.

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 hospitalisation or death from any cause through Day 28



Abbreviations: BMI=body mass index, COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (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 mAb 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.

Participants performed daily self-assessments of COVID-19 associated symptoms of cough, shortness of breath or difficulty breathing, feeling feverish, chills or shivering, muscle or body aches, diarrhoea, nausea, vomiting, headache, sore throat, stuffy or runny nose. The severity of each symptom was rated as absent, mild, moderate, or severe. Sustained symptom alleviation was defined as the first of 4 consecutive days when all of the above symptoms scored as moderate or severe at study entry were scored as mild or absent, and all of the above symptoms scored mild or absent at study entry were scored as absent. Sustained symptom resolution was defined as the time when all of the above symptoms were scored as absent for 4 consecutive days. Table 8 displays the results for time to sustained symptom alleviation and sustained symptom resolution in the mITT1 population. The Paxlovid group demonstrated superiority to the placebo group in both analyses.

Table 7: Analyses of Time to Sustained Symptom Alleviation and Sustained Symptom Resolution Through 28 Days (mITT1 Analysis Set): EPIC-HR

	Paxlovid (N=970)	**Placebo** (N=986)
Time to sustained symptom alleviation (days)[a] Median HR vs placebo (95% CI)[b] p-value	 13 1.266 (1.134, 1.412) <0.0001	 15

Time to sustained symptom resolution (days)[a]		
Median	16	19
HR vs placebo (95% CI)[b]	1.200 (1.068, 1.348)	
p-value	0.0022	

Abbreviations: CI=confidence interval; HR=hazard ratio; COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (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 mAb treatment and were treated ≤5 days after COVID-19 symptom onset); SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

a. Participants who were hospitalized for the treatment of COVID-19 or died during the 28-day period were considered as not achieving sustained symptom alleviation or resolution.

b. Evaluation was done in a Cox proportional hazard model with treatment and geographic region effects as independent variables, and symptom onset duration (≤3, >3 days), baseline SARS-CoV-2 serology status and baseline viral load (<4, ≥4 $\log_{10}$ copies/mL) as covariates.

The proportion of participants with any severe COVID-19 associated symptom was 22% in the Paxlovid group and 19% in the placebo group at baseline (Day 1), 17% and 18%, respectively, during treatment (from Day 2 to Day 6), and 8% and 11%, respectively, after treatment (from Day 7 to Day 28).

Efficacy in vaccinated participants with at least 1 risk factor for progression to severe COVID-19 illness (EPIC-SR)

EPIC-SR was 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 COVID-19 symptom onset of ≤5 days who were at standard risk for progression to severe disease. The study included previously unvaccinated participants without risk factors or fully vaccinated participants with at least 1 of the risk factors for progression to severe disease (as defined in the EPIC-HR section above and by local regulations and practices). A total of 1,296 participants were randomised (1:1) to receive Paxlovid or placebo orally every 12 hours for 5 days; of these, 49% were vaccinated at baseline with at least 1 risk factor for progression to severe disease.

Analyses of efficacy presented below is based on vaccinated participants with at least 1 risk factor for progression to severe disease. In vaccinated participants, Table 8 provides results of the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 (secondary endpoint of EPIC-SR). The relative risk reduction in the mITT1 analysis population for Paxlovid compared to placebo was 58%. The result did not reach statistical significance.

Table 8: Efficacy results in non-hospitalized vaccinated adults with at least 1 risk factor for progression to severe COVID-19 who were dosed within 5 days of symptom onset (mITT1 analysis set)

	Paxlovid (n=317)	**Placebo (n=314)**
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%)	3 (0.9%)	7 (2.2%)
Reduction relative to placebo[a] (95% CI), %	-1.292 (-3.255, 0.671)	
All-cause mortality through Day 28 %	0	1 (0.3%)

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; mITT1=modified intent-to-treat 1 (all participants randomly assigned to study intervention who took at least 1 dose of study intervention and with at least 1 post-baseline visit through Day 28).

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 hospitalisation and death status through Day 28 were censored at the time of study discontinuation.

Post-exposure prophylaxis (EPIC-PEP)

EPIC-PEP was a phase 2/3, randomised, double-blind, double-dummy, placebo-controlled study assessing the efficacy of Paxlovid (administered 5 days or 10 days) in post-exposure prophylaxis of COVID-19 in household contacts of symptomatic individuals infected with SARS-CoV-2. Eligible participants were asymptomatic adults 18 years of age and older who were SARS-CoV-2 negative at screening and who lived in the same household with symptomatic individuals with a recent diagnosis of SARS-CoV-2. A total of 2,736 participants were randomised (1:1:1) to receive Paxlovid orally every 12 hours for 5 days, Paxlovid orally every 12 hours for 10 days, or placebo.

Compared with placebo, the Paxlovid 5-day and 10-day regimens led to a 30% and 36% relative risk reduction, respectively, in the risk of developing a symptomatic, reverse transcriptase–polymerase chain reaction (RT-PCR) or rapid antigen test (RAT) confirmed SARS-CoV-2 infection through household contact; these results did not reach statistical significance. In a post hoc analysis, the risk of developing a symptomatic or asymptomatic confirmed SARS-CoV-2 infection was reduced by 31% and 35% with the Paxlovid 5-day and 10-day regimens, respectively, compared with placebo (Table 9).

Table 9: Efficacy results in symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection and symptomatic or asymptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection in participants exposed to SARS-CoV-2 through household contact (mITT analysis set)

	Paxlovid		**Placebo (N=840)**
	5 Days (N=844)	**10 Days (N=830)**	
Symptomatic, RT-PCR or RAT Confirmed SARS-CoV-2 Infection Through Day 14			
n (%)	22 (2.6%)	20 (2.4%)	33 (3.9%)
Relative risk reduction vs placebo (95% CI)	0.298 (-0.167, 0.578)	0.355 (-0.115, 0.627)	
p-value	0.1722	0.1163	
Symptomatic or Asymptomatic, RT-PCR or RAT Confirmed SARS-CoV-2 Infection Through Day 14[a]			
n (%)	39 (4.6%)	36 (4.3%)	59 (7.0%)
Relative risk reduction vs placebo (95% CI)	0.305 (-0.006, 0.520)	0.347 (0.044, 0.554)	
p-value	0.0535	0.0284	

Abbreviations: CI=confidence interval; mITT=all participants randomised to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline; RAT=rapid antigen test; RT-PCR=reverse transcriptase–polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

a. Post hoc analysis.

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

5.2 Pharmacokinetic properties

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy participants and in participants with mild-to-moderate COVID-19.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic (PK) enhancer resulting in higher systemic concentrations and longer half-life 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 plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to the time of last measurement (AUC_{last}) was 2.88 µg/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. Simulated repeat-dose exposures of nirmatrelvir/ritonavir 300 mg/100 mg administered twice daily in adult participants from EPIC-HR, suggested the mean AUC_{tau} was 28.3 µg*hr/mL, mean C_{max} was 3.29 µg/mL, and mean C_{min} was 1.40 µg/mL.

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 increased the exposure of nirmatrelvir (approximately 61% increase in mean C_{max} and 20% increase in mean AUC_{last}) relative to fasting conditions following administration of 300 mg nirmatrelvir (2 × 150 mg)/100 mg 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. Nirmatrelvir 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

Age and gender
In a population PK analysis, age and gender did not affect the pharmacokinetics of nirmatrelvir.

Racial or ethnic groups
Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants. In a population PK analysis, race did not affect the pharmacokinetics of nirmatrelvir.

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

Patients with hepatic impairment
Compared to healthy controls with no hepatic impairment, the pharmacokinetics of nirmatrelvir in participants with moderate hepatic impairment were 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.

Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

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 medicinal products that are primarily metabolised by CYP3A. Despite being coadministered with ritonavir as a PK enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of nirmatrelvir.

Interaction studies conducted with nirmatrelvir
In vitro data indicates that nirmatrelvir is a substrate for human MDR1 (P-gp) and CYP3A4, but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Nirmatrelvir does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro* at clinically relevant concentrations. Nirmatrelvir has the potential to reversibly and time dependently inhibit CYP3A4 and inhibit MDR1 (P-gp) and OATP1B1.

Nirmatrelvir does not induce any CYPs at clinically relevant concentrations.

Interaction studies conducted with ritonavir
In vitro studies indicate that ritonavir is mainly a substrate of CYP3A. Ritonavir also appears to be a substrate of CYP2D6 which contributes to the formation of isopropylthiazole oxidation metabolite M-2.

Ritonavir is an inhibitor of CYP3A and to a lesser extent CYP2D6. Ritonavir appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

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 10.

Table 10: Effects of coadministered medicinal products on pharmacokinetics of nirmatrelvir

Coadministered medicinal product	Dose (schedule)		N	Percent ratio of nirmatrelvir[a] PK parameters (90% CI); no effect=100	
	Coadministered medicinal product	Nirmatrelvir/ Ritonavir		C_{max}	AUC[b]
carbamazepine[c]	300 mg twice daily (16 doses)	300 mg/100 mg once daily (2 doses)	10	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}=observed maximum plasma concentrations; PK=pharmacokinetic.
a. Percent ratio of test (i.e., carbamazepine or itraconazole in combination with nirmatrelvir/ritonavir)/reference (i.e., nirmatrelvir/ritonavir alone).
b. For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.
c. 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 coadministration of Paxlovid with oral midazolam (CYP3A4 substrate), dabigatran (P-gp substrate), or rosuvastatin (OATP1B1 substrate) on the midazolam, dabigatran, and rosuvastatin AUC_{inf} and C_{max}, respectively, are summarized in Table 11.

Table 11: Effect of nirmatrelvir/ritonavir on pharmacokinetics of coadministered medicinal products

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_{inf}
midazolam[b] (oral)	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)

dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (4 doses)	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)
rosuvastatin[b]	10 mg (1 dose)	300 mg/100 mg twice daily (3 doses)	12	212.44 (174.31, 258.90)	131.18 (115.89, 148.48)

Abbreviations: AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum plasma concentrations; CYP3A4=cytochrome P450 3A4; OATP1B1=organic anion transporting polypeptide 1B1; P-gp=p-glycoprotein.

a. Percent ratio of test (i.e., midazolam, dabigatran, or rosuvastatin in combination with nirmatrelvir/ritonavir)/reference (i.e., midazolam, dabigatran, or rosuvastatin alone).
b. 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. For rosuvastatin, Test=nirmatrelvir/ritonavir plus rosuvastatin, Reference=rosuvastatin. Rosuvastatin is an index substrate for OATP1B1.

5.3 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 proteinuria were noted in rats and are considered 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 5× clinical exposures at the approved dose of Paxlovid.

Embryo-foetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and GD 7 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 9× higher than clinical exposures at the approved human dose of Paxlovid. In the rabbit EFD study, lower foetal body weights (9% decrease) were observed at 1000 mg/kg/day in the absence of significant maternal toxicity findings. At 1000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 11× higher than clinical exposures at the approved human dose of Paxlovid. No other significant developmental toxicities (malformations and embryo-foetal lethality) were observed at up to the highest dose tested, 1000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3× higher than clinical exposures at the approved human dose of Paxlovid.

In the pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9× higher than clinical exposures at the approved human dose of Paxlovid. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6× higher than clinical exposures at the approved human dose of Paxlovid.

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 in rats and 6 through 19 in rabbits). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) 5× (rats) or 8× (rabbits) higher than exposure at the approved human dose of Paxlovid. 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, at systemic exposures approximately 10× higher than exposure at the approved human dose of Paxlovid. In rabbits, resorptions, decreased litter size and decreased foetal weights were observed at maternally toxic doses, at systemic exposures greater than 8× higher than exposure at the approved human dose of Paxlovid. In a pre- and post-natal development study in rats, administration 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through Postnatal Day 20 resulted in no developmental toxicity, at ritonavir systemic exposures greater than 10× the exposure at the approved human dose of Paxlovid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of 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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the outer carton for shelf-life.

6.4 Special precautions for storage

Store below 25°C.

Do not refrigerate or freeze.

6.5 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.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Nirmatrelvir

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell
Newbridge,
Co. Kildare, W12 HX57,
Ireland (IRL)

Ritonavir

M/s. Hetero Labs Limited, Unit-III, 22-110,
Industrial Development Area, Jeedimetla,
Hyderabad-500055, Telangana, India

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