ENGLISH LEAFLET

Paxlovid™

1. NAME OF THE MEDICINAL PRODUCT

Paxlovid 150 mg/100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pink nirmatrelvir film-coated tablet contains 150 mg of nirmatrelvir.
Each white to off 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 (tablet).
Pink, oval, with a dimension of approximately 17.6 mm in length and 8.6 mm in width debossed with ‘PFE’ on one side and ‘3CL’ on the other side.

Ritonavir

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paxlovid is indicated for the treatment of COVID-19 in patients with 18 years of age and older who do not require supplemental oxygen and who are at high risk for progression to severe COVID-19 (see section 4.2 and 5.1 for posology and method of administration and patient selection).

4.2 Posology and method of administration

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer 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 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.

Usage limitation
Do not take Paxlovid more than 5 consecutive days because there is no safety and efficacy study support.

Do not use Paxlovid before or after exposure for purpose of COVID-19 prevention.

Do not use Paxlovid in another indication that is not for COVID-19 treatment.

If forget to take medicine
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.

Patient selection

The following medical conditions or other factors may place adult patients 18 years of age and older at high risk for progression to severe COVID-19.

- Older age (e.g., 60 years of age and older)
- Obesity or being overweight (e.g., body mass index [BMI] > 25 kg/m^2)
- Current smoker
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung disease (e.g., chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Active cancer
- Medical-related technological dependence not related to COVID-19 (e.g., tracheostomy, gastrostomy or positive pressure ventilation)

Other medical conditions or factors (e.g., race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and the approved use of Paxlovid is not limited to the medical conditions or factors listed above. Healthcare providers should consider the benefit-risk for an individual patient.

Special populations

Paediatric population

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

Elderly

No dose adjustment is currently recommended for elderly patients.

Renal impairment

No dose adjustment is needed in patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/minute). In patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/minute), the dose of Paxlovid should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements (see section 6.6).

Paxlovid is contraindicated in patients with severe renal impairment (eGFR < 30 ml/minute) 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 dose adjustment is needed; the dose of Paxlovid is 300 mg/100 mg twice daily for 5 days. Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated.

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 (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

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

Medicinal product class	Medicinal products within class	Clinical comments
		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.

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

Medicinal product class	Medicinal products within class	Clinical comments
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.
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
GI motility agent	cisapride	Increased plasma concentrations of cisapride, thereby increasing the risk of serious arrhythmias from this agent.
Immunosuppressants	voclosporin	Increased plasma concentrations of immunosuppressant.
Lipid-modifying agents		
HMG-CoA reductase inhibitors	lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin resulting in increased risk of myopathy, including rhabdomyolysis.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	Increased plasma concentrations of lomitapide.

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

Medicinal product class	**Medicinal products within class**	**Clinical comments**
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.
Antimycobacterials	rifampicin	Potentially decreased plasma concentrations of nirmatrelvir/ritonavir

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

Medicinal product class	Medicinal products within class	Clinical comments
		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.

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.

Co-administration 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 co-administration by closely and regularly monitoring immunosuppressant serum 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 co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Excipients

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Medicinal products listed in Table 1 (section 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, ↑dexamfetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are co-administered with Paxlovid.
Analgesics	↑buprenorphine (57%, 77%), ↑norbuprenorphine (33%, 108%)	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when

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
		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 SmPC for more information.
	↓methadone (36%, 38%)	Increased methadone dose may be necessary when co-administered 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.

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
	↓morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered 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 co-administration 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 co-administered with ritonavir, due to induction of CYP1A2.

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
Anticancer agents	↑afatinib	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and Cmax depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with Paxlovid (refer to the afatinib SmPC). Monitor for ADRs related to afatinib.
	↑abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and Paxlovid should be avoided. If this co-administration is judged unavoidable, refer to the abemaciclib SmPC for dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
	↑apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when co-administered with ritonavir resulting in the potential for serious

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
		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 SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑dasatinib, ↑nilotinib, ↑vincristine, ↑vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑encorafenib	Serum concentrations of encorafenib may be increased when co-administered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Co-administration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑fostamatinib	Co-administration 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 SmPC 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. Co-administration 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

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
		(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 SmPC). 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 SmPC 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 co-administration of apixaban with Paxlovid depend on the apixaban dose. Refer to the apixaban SmPC 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

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
		the dabigatran SmPC 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 co-administration of vorapaxar with Paxlovid is not recommended (refer to the vorapaxar SmPC).
	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 co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with ritonavir.

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

Medicinal product class	**Medicinal product within class (AUC change, C_{max} Change)**	**Clinical comments**
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	Co-administration 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 co-administered with ritonavir.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
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 co-administered with ritonavir.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Anti-gout	↑colchicine	Concentrations of colchicine are expected to increase when co-administered 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 co-administered with ritonavir.
Anti-infectives	↑fusidic acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).

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
	↑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 co-administered with ritonavir as a pharmacokinetic enhancer.
	rifampicin	Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. Concomitant use of rifampicin with Paxlovid is contraindicated (see section 4.3).
	↓voriconazole (39%, 24%)	Co-administration 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.
	↑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 co-administered with ritonavir.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑itraconazole[a], ↑erythromycin	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is co-administered with ritonavir.
	↓atovaquone	Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is co-administered with ritonavir.
	↑bedaquiline	No interaction study is available with ritonavir only. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline

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
		SmPC)
	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 co-administration 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 SmPC).
	rifapentine	May lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. Avoid concomitant use with Paxlovid.
	↑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 co-administered with ritonavir dosed as a pharmacokinetic enhancer. For

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
		patients with moderate renal impairment, the dose should be reduced by 50%. Paxlovid is contraindicated in patients with severe renal impairment (see sections 4.2 and 4.3).
	sulfamethoxazole/trimethoprim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
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 SmPC 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 SmPC 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 co-administered with ritonavir.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑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 SmPC 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.

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
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 co-administration 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.

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**
Benign prostatic hyperplasia agents	↑silodosin	Co-administration 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.

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
Cardiovascular agents	↑eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalaemia (see section 4.3).
	↑ivabradine	Co-administration 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	Co-administration 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 SmPC for more 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
Corticosteroids primarily metabolized by CYP3A	↑betamethasone, ↑budesonide, ↑ciclesonide, ↑fluticasone, ↑methylprednisolone, ↑mometasone, ↑triamcinolone	Co-administration 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.

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
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	Co-administration contraindicated due to potential loss of virologic response and possible resistance (see section 4.3).
	↑ivacaftor, ↑elexacaftor/tezacaftor/ivacaftor, ↑tezacaftor/ivacaftor	Reduce dosage when co-administered with Paxlovid. Refer to the individual product SmPC for more information.
Dipeptidyl peptidase 4 (DPP4) inhibitors	↑saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin SmPC for more information.
Endothelin antagonists	↑bosentan	Co-administration of bosentan and ritonavir may increase steady-state bosentan C_{max} and AUC.
Ergot derivatives	↑dihydroergotamine, ↑ergonovine, ↑ergotamine, ↑methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 4.3)

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**
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.

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**
HMG Co-A 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	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.

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

Medicinal product class	**Medicinal product within class (AUC change, C_{max} Change)**	**Clinical comments**
Hormonal contraceptive	↓ethinylestradiol (40%, 32%)	Due to reductions in ethinyl-estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered 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.

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
Immunosupressants	↑voclosporin	Co-administration 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 reaction are recommended during and after treatment with Paxlovid. Refer to the individual immunosuppressant SmPC and latest guidelines for further information and obtain expert consultation of a multidisciplinary group (see section 4.4).

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
Janus kinase (JAK) inhibitors	↑tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib SmPC for more information.
	↑upadacitinib	Dosing recommendations for co-administration of upadacitinib with Paxlovid depends on the upadacitinib indication. Refer to the upadacitinib SmPC 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) inhibitors	↑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 (see SmPC for lomitapide) (see section 4.3).

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
Migraine medications	↑eletriptan	Co-administration 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	Co-administration 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	Co-administration 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 co-administered with Paxlovid. Refer to the darifenacin SmPC for more 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
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 SmPC for more 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**
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 SmPC for more information.
	↑vardenafil (49-fold, 13-fold)	Concomitant use of vardenafil with Paxlovid is contraindicated (see section 4.3).

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
PDE5 inhibitors (Pulmonary hypertension agents)	↑sildenafil (Revatio®)	Co-administration 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 SmPC for more information.
Opioid antagonists	↑naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms (see section 4.3).
Sedatives/hypnotics	↑oral (1430%, 368%) and parenteral midazolam[a]	Midazolam is extensively metabolised by CYP3A4. Co-administration 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 co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with

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
		co-administration 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 co-administered 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 co-administration 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 co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic

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
		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 drugs when co-administered 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 co-administered with careful monitoring for excessive sedative effects.
Serotonin receptor 1A agonists/ serotonin receptor 2A antagonists	↑flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression (see section 4.3).

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
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 co-administration.
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.

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
Vasopressin receptor antagonists	↑tolvaptan	Co-administration 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 no human data on the use of Paxlovid during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid.

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 post-natal 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

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

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

Fertility

There are no human data on the effect of Paxlovid on fertility. No human data on the effect of nirmatrelvir on fertility are available. Nirmatrelvir produced no effects on fertility in rats (see 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 is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomised, placebo-controlled trial in non-hospitalised adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection (see section 5.1). A total of 2,224 symptomatic adult participants 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) (n=1,109) or placebo (n=1,115). Study drugs were to be taken twice daily for up to 5 days.

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

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common ($\geqslant$ 1/10); common ($\geqslant$ 1/100 to < 1/10); uncommon ($\geqslant$ 1/1,000 to < 1/100); rare ($\geqslant$ 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, direct acting antivirals, ATC code: not yet assigned.

Mechanism of action

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

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

Antiviral activity

In vitro antiviral activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line (EC90 value of 181 nM) after Day 3 post-infection.

In vivo antiviral activity

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

Antiviral resistance

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

Pharmacodynamic effects

Cardiac electrophysiology

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

Clinical efficacy and safety

The efficacy of Paxlovid is based on the interim analysis and the supporting 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. Eligible participants were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or

immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Participants with COVID-19 symptom onset of $\leqslant$ 5 days were included in the study. The study excluded individuals with a history of prior COVID-19 infection or vaccination.

Participants were randomised (1:1) to receive Paxlovid (nirmatrelvir 300 mg/ritonavir 100 mg) or placebo orally every 12 hours for 5 days. The primary efficacy endpoint was the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated subjects with onset of symptoms $\leqslant$ 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 subjects with onset of symptoms $\leqslant$ 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 subjects with onset of symptoms $\leqslant$ 5 days).

A total of 2,246 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 46 years with 13% of participants 65 years of age and older (3% were 75 years of age and older); 51% were male; 72% were White, 5% were Black, and 14% were Asian; 45% were Hispanic or Latino; 66% of participants had onset of symptoms $\leqslant$ 3 days from initiation of study treatment; 81% had a BMI $\geq$ 25 kg/m^2 (37% a BMI $\geq$ 30 kg/m^2); 12% had diabetes mellitus; less than 1% of the study population had immune deficiency, 47% of participants were serological negative at baseline and 51% were serological positive. The mean (SD) baseline viral load was 4.63 $\log_{10}$ copies/mL (2.87); 26% of participants had a baseline viral load of > 10^7 (copies/mL); 6.2% 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 primary SARS-CoV-2 variant across both treatment arms was Delta (98%), mostly clade 21J (based on interim analysis).

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

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of

(-9.0%, -3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was <0.0001 with 2-sided significance level of 0.002.

Table 4 provides results of the primary endpoint in the mITT1 analysis population for the full data set at final study completion.

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

	Paxlovid (N=1,039)	**Placebo (N=1,046)**
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%) Reduction relative to placebo[a] [95% CI], %	8 (0.8%) -5.62 (-7.21, -4.03)	66 (6.3%)
All-cause mortality through Day 28, %	0	12 (1.1%)

Abbreviations: CI=confidence interval.

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 subjects without hospitalisation and death status through Day 28 were censored at the time of study discontinuation.

The estimated risk reduction was -5.8% with 95% CI of (-7.8%, -3.8%) in participants dosed within 3 days of symptom onset, and –5.2% with 95% CI of (-7.9%, -2.5%) in the mITT1 subset of participants dosed > 3 days from symptom onset.

Consistent results were observed in the final mITT and mITT2 analysis populations. A total of 1,379 subjects were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the Paxlovid group, and 44/682 (6.45) in the placebo group.

Table 5: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 analysis set

	Paxlovid 300 mg/100 mg	Placebo
Number of patients	N=1,039	N=1,046
Serology Negative	n=487	n=505
Patients with hospitalisation or death[a] (%)	7 (1.4%)	58 (11.5%)
Estimated proportion over 28 days [95% CI], %	1.47 (0.70, 3.05)	11.71 (9.18, 14.89)
Reduction relative to placebo [95% CI]	-10.25 (-13.28, -7.21)	
p-value	p<0.0001	
Serology Positive	n=540	n=528
Patients with hospitalisation or death[a] (%)	1 (0.2%)	8 (1.5%)
Estimated proportion over 28 days [95% CI], %	0.19 (0.03, 1.31)	1.52 (0.76, 3.02)
Reduction relative to placebo [95% CI]	-1.34 (-2.45, -0.23)	
p-value	p=0.0180	

Abbreviations: CI=confidence interval; mITT=modified intent-to-treat. All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 5 days after COVID-19 symptom onset.

Seropositivity was defined if results were positive in a serological immunoassay specific for host antibodies to either S or N viral proteins.

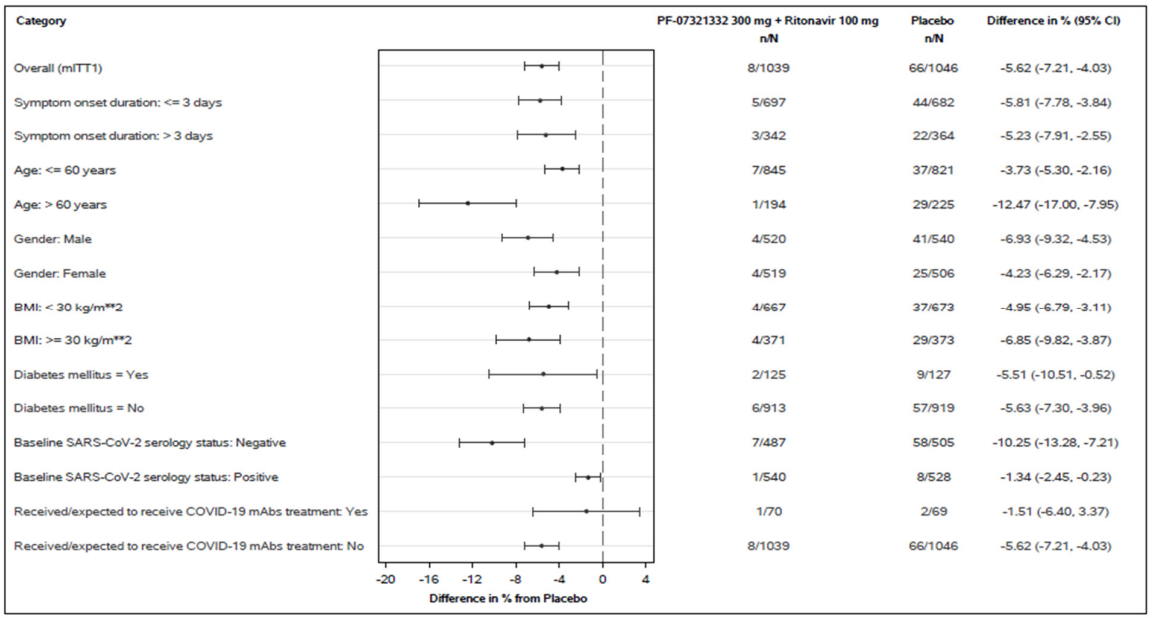
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.

a. COVID-19 related hospitalisation or death from any cause.

Efficacy results for mITT1 were consistent across subgroups of participants including age (⩾ 65 years) and BMI (BMI > 25 and BMI > 30) and diabetes.

These subgroup analyses are considered exploratory.

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 (Protocol C4671005)



5.2 Pharmacokinetic properties

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

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

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

Absorption

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

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

Effect of food on oral absorption

Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir co-administered with ritonavir tablets.

Distribution

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

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

Biotransformation

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

observed was unchanged nirmatrelvir. Minor oxidative metabolites were observed in the faeces and urine.

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

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

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

Elimination

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact drug. Approximately 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and faeces, respectively. 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

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

Racial or ethnic groups

Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants.

Patients with renal impairment

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

Table 6: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	**Mild Renal Impairment (n=8)**	**Moderate Renal Impairment (n=8)**	**Severe Renal Impairment (n=8)**
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 - 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 - 6.1)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Patients with hepatic impairment

Compared to healthy controls with no hepatic impairment, the pharmacokinetics of nirmatrelvir in subjects with moderate hepatic impairment was not significantly different.

Table 7: Impact of Hepatic Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Hepatic Function (n=8)	**Moderate Hepatic Impairment (n=8)**
C_{max} (µg/mL)	1.89 (20)	1.92 (48)
AUC_{inf} (µg*hr/mL)	15.24 (36)	15.06 (43)
T_{max} (hr)	2.0 (0.6 - 2.1)	1.5 (1.0 - 2.0)
$T_{1/2}$ (hr)	7.21 ± 2.10	5.45 ± 1.57

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

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 drugs that are primarily metabolised by CYP3A. Despite being co-administered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of nirmatrelvir.

The effects of co-administration of Paxlovid with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarised in Table 8 (effect of other medicinal products on nirmatrelvir).

Table 8: Interactions with other medicinal products: pharmacokinetic parameters for nirmatrelvir in the presence of the co-administered medicinal products

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

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

a. For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.

Table 8: Interactions with other medicinal products: pharmacokinetic parameters for nirmatrelvir in the presence of the co-administered medicinal products

Co-administered medicinal product	Dose (schedule)		N	Ratio (in combination with co-administered medicinal product/alone) of nirmatrelvir pharmacokinetic parameters (90% CI); no effect=100	
	Co-administered medicinal product	Nirmatrelvir/ ritonavir		C_{max}	AUC[a]

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g. 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

The effects of co-administration of Paxlovid with oral midazolam (CYP3A4 substrate) or dabigatran (P-gp substrate) on the midazolam and dabigatran AUC and C_{max}, respectively, are summarized in Table 9.

Table 9: Effect of nirmatrelvir/ritonavir on pharmacokinetics of co-administered drug

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

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

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

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 proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Carcinogenesis

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

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

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

Mutagenesis

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

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

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

Reproductive toxicity

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

The potential embryo-foetal toxicity of nirmatrelvir was evaluated in the definitive rat and rabbit studies at doses up to 1,000 mg/kg/day. There was no nirmatrelvir-related effect in any of the parameters in the rat embryo-foetal development (EFD) study up to the highest dose of 1,000 mg/kg/day (exposure margin of 16x/7.8x based on total C_{max}/AUC_{24} over the predicted human exposures at a dose of 300 mg/100 mg nirmatrelvir/ritonavir twice daily). In the rabbit EFD study, there was no nirmatrelvir-related effect on foetal morphology or embryo-foetal viability up to the highest dose of 1,000 mg/kg/day (exposure margin of 24x/10x based on total C_{max}/AUC_{24}),

however adverse nirmatrelvir-related lower foetal body weights (0.91x control) were observed at 1,000 mg/kg/day in the presence of nonadverse, low magnitude effects on maternal body weight change and food consumption at this dose. Growth delay is likely reversible following cessation of exposure in human, and it was not present at the intermediate dose (10x/2.8x C_{max}/AUC_{24} over the predicted clinical exposure). There were no nirmatrelvir-related severe manifestations of developmental toxicity (malformations and embryo-foetal lethality) at the highest dose tested, 1,000 mg/kg/day.

Ritonavir

Ritonavir produced no effects on fertility in rats.

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

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

2 years.

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

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer (Thailand) Limited

8. MARKETING AUTHORISATION NUMBERS

2C 1/65 (NC)

9. DATE OF AUTHORIZATION

28 January 2022

10. DATE OF REVISION OF THE TEXT

7 February 2024