ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Paxlovid 150 mg + 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pink film-coated tablet contains 150 mg of nirmatrelvir.
Each white film-coated tablet contains 100 mg of ritonavir.

Excipients with known effect

Each pink 150 mg film-coated tablet of nirmatrelvir 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 coronavirus disease 2019 (COVID-19) in adults and paediatric patients 6 years of age and older weighing at least 20 kg who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 (see section 5.1).

4.2 Posology and method of administration

Posology

Adults
The recommended dose in adults is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days.

Paediatric patients 6 years of age and older weighing at least 20 kg
The recommended dose in paediatric patients 6 years of age and older weighing at least 20 kg is shown below in Table 1.

Table 1: Recommended dose for paediatric patients 6 years of age and older weighing at least 20 kg

Patient population	Recommended dose
Paediatric patients ≥6 years of age weighing ≥40 kg	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days
Paediatric patients ≥6 years of age weighing ≥20 to <40 kg	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) taken together orally every 12 hours for 5 days

Special attention for paediatric patients 6 years of age and older weighing at least 20 kg to less than 40 kg
There is a pack specific for paediatric patients 6 years of age and older weighing at least 20 kg to less than 40 kg. This pack contains 5 blister cards with two separated parts each containing one tablet of nirmatrelvir and one tablet of ritonavir for administration every 12 hours.

Paxlovid should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset. Completion of the full 5-day treatment course is recommended even if the patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with this medicinal product.

If the patient misses a dose within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Special populations

Renal impairment
No dose adjustment is needed in patients with mild renal impairment [estimated glomerular filtration rate (eGFR) ≥ 60 to < 90 mL/min]. In adult patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min) or with severe renal impairment [eGFR < 30 mL/min, including patients with End Stage Renal Disease (ESRD) under haemodialysis], the dose should be reduced as shown in Table 2 to avoid over-exposure. The treatment should be administered at approximately the same time each day for 5 days. On days patients with severe renal impairment undergo haemodialysis, the dose should be administered after haemodialysis (see section 5.2).

Table 2: Recommended dose and regimen for adult patients with renal impairment

Renal function	Days of treatment	Dose and dose frequency
Moderate renal impairment (eGFR ≥ 30 to < 60 mL/min)	Days 1-5	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) **every 12 hours**
Severe renal impairment (eGFR < 30 mL/min) including those requiring haemodialysis	Day 1	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) **once**
	Days 2-5	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) **once daily**

Abbreviation: eGFR=estimated glomerular filtration rate.

Special attention for patients with MODERATE renal impairment
There is a pack specific for patients with moderate renal impairment. This pack contains 5 blister cards with two separated parts each containing one tablet of nirmatrelvir and one tablet of ritonavir for administration every 12 hours.

Special attention for patients with SEVERE renal impairment
There is a pack specific for patients with severe renal impairment. This pack contains 1 blister card with one separated part containing two tablets of nirmatrelvir and one tablet of ritonavir for administration once on Day 1, and four additional separated parts each containing one tablet of nirmatrelvir and one tablet of ritonavir for administration once daily on Days 2 to 5.

Although the safety and pharmacokinetics of nirmatrelvir/ritonavir have not been studied in paediatric patients with renal impairment, dose reduction in paediatric patients 6 years of age and older weighing at least 40 kg with renal impairment should parallel that recommended for adults with the same degree of renal impairment (see Table 2) (see section 5.2).

Dose in paediatric patients with renal impairment weighing less than 40 kg has not been determined.

Hepatic impairment
No dose adjustment is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Paxlovid should not be used in patients with severe (Child-Pugh Class C) hepatic impairment (see sections 4.4 and 5.2).

Severely immunocompromised population
Data are limited in severely immunocompromised individuals. A treatment duration of 10 days may help to mitigate the risk of virological rebound in patients with severe immunodepression (e.g. active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) (see section 5.1).

Concomitant therapy with ritonavir- or cobicistat-containing regimen
No dose adjustment is needed. 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.

Paediatric population
The safety and efficacy of Paxlovid in paediatric patients below 6 years of age or weighing less than 20 kg have not been established.

Paediatric dosing for paediatric patients 6 years of age and older weighing at least 20 kg is based on the results from a paediatric study (see sections 5.1 and 5.2).

Method of administration

For oral use.

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

This medicinal product can be taken with or without food (see section 5.2). The tablets should be swallowed whole and not chewed, broken or crushed, as no data is currently available.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Medicinal products listed below are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated with Paxlovid.

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.

- Alpha$_1$-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: dronedarone, propafenone, quinidine
- Anticancer drugs: neratinib, venetoclax
- Anti-gout: colchicine
- Antihistamines: terfenadine
- Antipsychotics/neuroleptics: lurasidone, pimozide, quetiapine
- Benign prostatic hyperplasia medicinal products: silodosin
- Cardiovascular medicinal products: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine
- GI motility agents: cisapride
- Immunosuppressants: voclosporin
- Lipid-modifying agents:
    - HMG Co-A reductase inhibitors: lovastatin, simvastatin
    - Microsomal triglyceride transfer protein (MTTP) inhibitor: lomitapide
- Migraine medicinal products: eletriptan
- Mineralocorticoid receptor antagonists: finerenone
- Neuropsychiatric agents: cariprazine
- Opioid antagonists: naloxegol
- PDE5 inhibitor: avanafil, sildenafil, tadalafil, vardenafil
- Sedative/hypnotics: clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam
- Vasopressin receptor antagonists: tolvaptan

Medicinal products that are potent CYP3A inducers where significantly reduced nirmatrelvir/ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

- Antibiotics: rifampicin, rifapentine
- Anticancer drugs: apalutamide, enzalutamide
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin, primidone
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St. John's wort (*Hypericum perforatum*)

Paxlovid cannot be started immediately after discontinuation of CYP3A4 inducers due to the delayed offset of the recently discontinued CYP3A4 inducer (see section 4.5).

A multi-disciplinary approach (e.g., involving physicians and specialists in clinical pharmacology) should be considered to determine the adequate timing for Paxlovid initiation taking into account the delayed offset of the recently discontinued CYP3A inducer and the need to initiate Paxlovid within 5 days of symptom onset.

4.4 Special warnings and precautions for use

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

Management of drug-drug interactions (DDIs) in high-risk COVID-19 patients receiving multiple concomitant medications can be complex and require a thorough understanding of the nature and magnitude of interaction with all concomitant medications. In certain patients, a multi-disciplinary approach (e.g., involving physicians and specialists in clinical pharmacology) should be considered for

management of DDIs especially if concomitant medications are withheld, their dose is reduced, or if monitoring of side effects is necessary.

Effects of Paxlovid on 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 (see section 4.5).

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).

Effects of other medicinal products on Paxlovid
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 with 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 3 for medicinal products that are contraindicated for concomitant use with nirmatrelvir/ritonavir and 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.

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 this medicinal product and initiate appropriate medications and/or supportive care.

Severe hepatic impairment

No pharmacokinetic and clinical data are available in patients with severe hepatic impairment. Therefore, this medicinal product should not be used in patients with severe hepatic impairment.

Hepatotoxicity

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

Elevation in blood pressure

Cases of hypertension, generally non serious and transient, have been reported during treatment with Paxlovid. Specific attention including regular monitoring of blood pressure should be paid notably to elderly patients since they are at higher risk of experiencing serious complications of hypertension.

Risk of HIV-1 resistance development

Because 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 medicinal product.

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

Effect of other medicinal products on Paxlovid

Nirmatrelvir and ritonavir are CYP3A substrates.

Coadministration of Paxlovid with medicinal products that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce Paxlovid therapeutic effect.

Coadministration of Paxlovid with medicinal product that inhibits CYP3A4 may increase nirmatrelvir and ritonavir plasma concentrations.

Effects of Paxlovid on other medicinal products

Medicinal products CYP3A4 substrates
Paxlovid (nirmatrelvir/ritonavir) is a strong inhibitor of CYP3A and increases plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Thus, coadministration of nirmatrelvir/ritonavir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see Table 3). Coadministration of other CYP3A4 substrates that may lead to potentially significant interaction (see Table 3) should be considered only if the benefits outweigh the risks.

Medicinal products CYP2D6 substrates
Based on *in vitro* studies, ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Coadministration of Paxlovid with drug substrates of CYP2D6 may increase the CYP2D6 substrate concentration.

Medicinal products P-glycoprotein substrates
Paxlovid also has a high affinity for P-glycoprotein (P-gp) and inhibits this transporter; caution should thus be exercised in case of concomitant treatment. Close drug monitoring for safety and efficacy should be performed, and dose reduction may be adjusted accordingly, or avoid concomitant use.

Paxlovid may induce glucuronidation and oxidation by CYP1A2, CYP2B6, 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.

Based on *in vitro* studies there is a potential for nirmatrelvir to inhibit MDR1 and OATP1B1 at clinically relevant concentrations.

Dedicated drug-drug interactions studies conducted with Paxlovid indicate that the drug interactions are primarily due to ritonavir. Hence, drug interactions pertaining to ritonavir are applicable for Paxlovid.

Medicinal products listed in Table 3 are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated or may interact with nirmatrelvir/ritonavir.

Table 3: 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	Tamsulosin is extensively metabolised, mainly by CYP3A4 and CYP2D6, both of which are inhibited by ritonavir. Avoid concomitant use with Paxlovid.
Amphetamine derivatives	↑Amphetamine	Ritonavir administered at high dose in accordance with its previous use as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are coadministered with Paxlovid.
Analgesics	↑Buprenorphine (57%, 77%)	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, ↑Oxycodone	Ritonavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of these narcotic analgesics. If concomitant use with Paxlovid is necessary, consider a dose reduction of these narcotic analgesics and closely monitor therapeutic and adverse effects (including respiratory depression). Refer to the individual SmPCs 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. Monitor methadone-maintained patients closely for evidence of withdrawal effects. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.

Table 3: 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 coadministered ritonavir dosed as a pharmacokinetic enhancer.
	↑Pethidine	Coadministration could result in increased or prolonged opioid effects. If concomitant use is necessary, consider dose reduction of pethidine. Monitor for respiratory depression and sedation.
	↓Piroxicam	Decreased piroxicam exposure due to CYP2C9 induction by Paxlovid.
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 ↑Flecainide	Given the risk of substantial increase in amiodarone or flecainide exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
	↑Digoxin	This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer. Digoxin drug concentration is expected to increase. Monitor digoxin levels if possible and digoxin safety and efficacy.
	↑Disopyramide	Ritonavir may increase plasma concentrations of disopyramide which could result in an increased risk of adverse events such as cardiac arrhythmias. Caution is warranted and therapeutic concentration monitoring is recommended for disopyramide if available.
	↑Dronedarone, ↑Propafenone, ↑Quinidine	Ritonavir coadministration is likely to result in increased plasma concentrations of dronedarone, propafenone and quinidine and is therefore contraindicated (see section 4.3).
Antiasthmatic	↓Theophylline (43%, 32%)	An increased dose of theophylline may be required when coadministered with ritonavir, due to induction of CYP1A2.
Anticancer agents	↑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 SmPC for dose adjustment recommendations. Monitor for ADRs related to abemaciclib.

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑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 C_{max} 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.
	↑Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when coadministered with ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of Paxlovid with apalutamide is contraindicated (see section 4.3).
	↑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 dose adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑Dasatinib, ↑Nilotinib, ↑Vinblastine, ↑Vincristine	Serum concentrations may be increased when coadministered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑Encorafenib, ↑Ivosidenib	Serum concentrations of encorafenib or ivosidenib 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. Avoid coadministration of encorafenib or ivosidenib. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.
	Enzalutamide	Enzalutamide is a strong CYP3A4 inducer, and this may lead to decreased exposure of Paxlovid, potential loss of virologic response, and possible resistance. Concomitant use of enzalutamide with Paxlovid is contraindicated (see section 4.3).
	↑Fostamatinib	Coadministration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		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. 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 and is therefore contraindicated (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 to 100 mg or less (or by at least 75% if already modified for other reasons) when used with strong CYP3A inhibitors.
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. For apixaban doses of 5 mg or 10 mg twice daily, reduce the apixaban dose by 50%. In patients already taking apixaban 2.5 mg twice daily, avoid coadministration with Paxlovid.
	↑Dabigatran (94%, 133%)*	Concomitant administration of Paxlovid is expected to increase dabigatran concentrations resulting in increased risk of bleeding. Reduce dose of dabigatran or avoid concomitant use.
	↑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

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		risk. Therefore, the use of Paxlovid is not recommended in patients receiving rivaroxaban.
	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*, Phenobarbital, Phenytoin, Primidone	Carbamazepine decreases AUC and C_{max} of nirmatrelvir by 55% and 43%, respectively. Phenobarbital, phenytoin and primidone are strong CYP3A4 inducers, and this may lead to a decreased exposure of nirmatrelvir and ritonavir and potential loss of virologic response. Concomitant use of carbamazepine, phenobarbital, phenytoin and primidone with Paxlovid is contraindicated (see section 4.3).
	↑Clonazepam	A dose decrease may be needed for clonazepam when coadministered with Paxlovid and clinical monitoring is recommended.
	↓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.
Anticorticosteroids	↑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.
Antidepressants	↑Amitriptyline, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Sertraline	Ritonavir administered at high dose in accordance with its previous use as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.

Table 3: 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 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).
Anti-HCV	↑Glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-gp, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and Paxlovid is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
	↑Sofosbuvir/velpatasvir/ voxilaprevir	Serum concentrations may be increased due to OATP1B inhibition by ritonavir. Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and Paxlovid is not recommended. Refer to the sofosbuvir/velpatasvir/voxilaprevir SmPC for further information.
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.
	↑Terfenadine	Increased plasma concentrations of terfenadine. Thereby, increasing the risk of serious arrhythmias from this agent and therefore concomitant use with Paxlovid is contraindicated (see section 4.3).
Anti-HIV	↑Bictegravir/ ↔Emtricitabine/ ↑Tenofovir	Ritonavir may significantly increase the plasma concentrations of bictegravir through CYP3A inhibition. Ritonavir is expected to increase the absorption of tenofovir alafenamide by inhibition of P-gp, thereby increasing the systemic concentration of tenofovir.
	↑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.

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		Refer to efavirenz SmPC for more information.
	↑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 Summary of Product Characteristics for maraviroc.
	↓Raltegravir (16%, 1%)	Coadministration of ritonavir and raltegravir results in a minor reduction in raltegravir levels.
	↓Zidovudine (25%, ND)	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.
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.
	↑Bedaquiline	No interaction study is available with ritonavir only. Due to the risk of bedaquiline related adverse events, coadministration should be avoided. If the benefit outweighs the risk, coadministration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline Summary of Product Characteristics).
	↑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 renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 mL/min the dose should be reduced by 50% (see section 4.2 for patients with severe renal impairment).
	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

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		risk of QTc prolongation associated with DM-6705, if coadministration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full Paxlovid treatment period is recommended (see section 4.4 and refer to the delamanid Summary of Product Characteristics).
	↑Erythromycin, ↑Itraconazole*	Itraconazole increases AUC and C_{max} of nirmatrelvir by 39% and 19%, respectively. Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is coadministered with ritonavir.
	↑Fusidic acid (systemic route)	Given the risk of substantial increase in fusidic acid (systemic route) exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
	↑Rifabutin (4-fold, 2.5-fold), ↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold)	An increase in rifabutin exposure is expected due to the inhibition of CYP3A4 by ritonavir. The consultation of a multidisciplinary group is recommended to safely guide the co-administration and the need of a reduction of the rifabutin dose.
	Rifampicin, Rifapentine	Rifampicin and rifapentine are strong CYP3A4 inducers, and this may lead to a decreased exposure of nirmatrelvir/ritonavir, potential loss of virologic response and possible resistance. Concomitant use of rifampicin or rifapentine with Paxlovid is contraindicated (see section 4.3).
	Sulfamethoxazole/trimethoprim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
	↓Voriconazole (39%, 24%)	Coadministration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
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	↑Clozapine	Given the risk of increase in clozapine exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
	↑Haloperidol, ↑Risperidone, ↑Thioridazine	Ritonavir is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
	↑Lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see section 4.3).
	↑Pimozide	Ritonavir coadministration is likely to result in increased plasma concentrations of pimozide and is therefore 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).
Benign prostatic hyperplasia agents	↑Silodosin	Coadministration is contraindicated due to potential for postural hypotension (see section 4.3).
β2-agonist (long acting)	↑Salmeterol	Ritonavir inhibits CYP3A4 and as a result a pronounced increase in the plasma concentrations of salmeterol is expected, resulting in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Therefore, avoid concomitant use with Paxlovid.
Calcium channel antagonists	↑Amlodipine, ↑Diltiazem,	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑Felodipine, ↑Nicardipine, ↑Nifedipine, ↑Verapamil	inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Consultation of a multidisciplinary group should be obtained to guide on the best way to handle the drug interaction by dose decrease or even temporary discontinuation of calcium channel antagonist when coadministered with Paxlovid. Moreover, if coadministered, patients should be carefully monitored for therapeutic and adverse effects during the coadministration. Refer to individual calcium channel antagonist SmPCs for more information.
	↑Lercanidipine	Given the risk of significant increase in lercanidipine exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
Cardiovascular agents	↑Aliskiren	Avoid concomitant use with Paxlovid.
	↑Cilostazol	Dose adjustment of cilostazol is recommended. Refer to the cilostazol SmPC for more information.
	Clopidogrel	Coadministration with clopidogrel may decrease levels of clopidogrel active metabolite. Avoid concomitant use with Paxlovid.
	↑Eplerenone	Coadministration with eplerenone is contraindicated due to potential for hyperkalemia (see section 4.3).
	↑Ivabradine	Coadministration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances (see section 4.3).
	↑Ticagrelor	Given the risk of substantial increase in ticagrelor exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
Cystic fibrosis transmembrane conductance regulator potentiators	↑Elexacaftor/ tezacaftor/ivacaftor, ↑Ivacaftor, ↑Tezacaftor/ivacaftor	Reduce dose when coadministered with Paxlovid. Refer to individual SmPCs for more information.
	Lumacaftor/ivacaftor	Coadministration contraindicated due to potential loss of virologic response and possible resistance (see section 4.3).

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Dipeptidyl peptidase 4 (DPP4) inhibitors	↑Saxagliptin	Dose adjustment of saxagliptin to 2.5 mg once daily is recommended.
Endothelin antagonists	↑Bosentan	Coadministration of bosentan and ritonavir resulted in an increase of steady-state bosentan maximum concentrations (C_{max}) and AUC. Avoid concomitant use with Paxlovid. Refer to bosentan SmPC for more information.
	↑Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The coadministration of riociguat with Paxlovid is not recommended (refer to riociguat SmPC).
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).
GI motility agent	↑Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent and therefore concomitant use with Paxlovid is contraindicated (see section 4.3).
Herbal products	St. John's Wort	Herbal preparations containing St John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of nirmatrelvir and ritonavir and therefore concomitant use with Paxlovid is contraindicated (see section 4.3).
HMG Co-A reductase inhibitors	↑Lovastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir at high dose in accordance with its previous use as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see section 4.3).
	↑Atorvastatin, Rosuvastatin (31%, 112%)*	Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		lowest possible doses of atorvastatin or rosuvastatin should be administered.
	↑Fluvastatin, Pravastatin	While not dependent on CYP3A for metabolism, pravastatin and fluvastatin exposure may be increased due to transporter inhibition. Consider temporary discontinuation of pravastatin and fluvastatin during treatment with Paxlovid.
Hormonal contraceptive	↓Ethinyl Estradiol (40%, 32%)	Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant Paxlovid use 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 is contraindicated due to potential for acute and/or chronic nephrotoxicity (see section 4.3).
Immunosuppressants	Calcineurin inhibitors: ↑Cyclosporine, ↑Tacrolimus mTOR inhibitors: ↑Everolimus, ↑Sirolimus	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, everolimus, sirolimus and tacrolimus. This coadministration should only be considered with close and regular monitoring of immunosuppressant blood concentrations, to reduce the dose of the immunosuppressant in accordance with the latest guidelines and to avoid over-exposure and subsequent increase of serious adverse reactions of the immunosuppressant. It is important that the close and regular monitoring is performed not only during the coadministration with Paxlovid but is also pursued after the treatment with Paxlovid. As overall recommended for managing the drug-drug interaction, consultation of a multidisciplinary group is required to handle the complexity of this coadministration (see section 4.4).
Janus kinase (JAK) inhibitors	↑Tofacitinib	Dose adjustment of tofacitinib is recommended. Refer to the tofacitinib SmPC for more information.
	↑Upadacitinib	Dosing recommendations for coadministration of upadacitinib with Paxlovid depends on the upadacitinib indication. Refer to the upadacitinib SmPC for more information.

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Lipid-modifying agents	↑Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of Paxlovid with lomitapide is contraindicated (see prescribing information for lomitapide) (see section 4.3).
Migraine medicinal products	↑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).
	↑Rimegepant	Avoid concomitant use with Paxlovid.
Mineralocorticoid receptor antagonists	↑Finerenone	Coadministration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension and hyponatremia (see section 4.3).
Muscarinic receptor antagonists	↑Darifenacin	Given the risk of substantial increase in darifenacin exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
	↑Solifenacine	Given the risk of substantial increase in solifenacine exposure and thus of its related adverse events, coadministration should not be used unless a multidisciplinary consultation could be obtained to safely guide it.
Neuropsychiatric agents	↑Aripiprazole, ↑Brexpiprazole	Dose adjustment of aripiprazole and brexpiprazole is recommended. Refer to aripiprazole or brexpiprazole SmPCs for more information.
	↑Cariprazine	Coadministration is contraindicated due to increased plasma exposure of cariprazine and its active metabolites (see section 4.3).
Opioid antagonists	↑Naloxegol	Coadministration contraindicated due to the potential for opioid withdrawal symptoms (see section 4.3).
Phosphodiesterase (PDE5) inhibitors	↑Avanafil (13-fold, 2.4-fold), ↑Sildenafil (11-fold, 4-fold), ↑Tadalafil (124%, ↔), ↑Vardenafil (49-fold, 13-fold)	Concomitant use of avanafil, sildenafil, tadalafil and vardenafil with Paxlovid is contraindicated (see section 4.3).
Sedatives/hypnotics	↑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 at high dose

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		in accordance with its previous use as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
	↑Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.
	↑Clorazepate, ↑Diazepam, ↑Estazolam, ↑Flurazepam	Ritonavir coadministration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam, and flurazepam and is therefore contraindicated (see section 4.3).
	↑Oral Midazolam (1330%, 268%)* and parenteral Midazolam	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, coadministration of Paxlovid with orally administered midazolam is contraindicated (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- to 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. Dose 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).
Sleeping agent	↑Zolpidem (28%, 22%)	Zolpidem and ritonavir may be coadministered with careful monitoring for excessive sedative effects.
Smoke cessation	↓Bupropion (22%, 21%)	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels.

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		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.
Steroids	Budesonide, Inhaled, injectable or intranasal fluticasone propionate, Triamcinolone	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86%) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A e.g., budesonide and triamcinolone. Consequently, concomitant administration of ritonavir at high dose in accordance with its previous use as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.
	↑Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.
	↑Prednisolone (28%, 9%)	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by

Table 3: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		37% and 28% after 4 and 14 days ritonavir, respectively.
Thyroid hormone replacement therapy	Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.
Vasopressin receptor antagonists	↑Tolvaptan	Coadministration is contraindicated due to potential for dehydration, hypovolemia and hyperkalemia (see section 4.3).

Abbreviations: ATL=alanine aminotransferase; AUC=area under the curve.
* Results from DDI studies conducted with Paxlovid (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There are limited data on the use of Paxlovid in pregnant women to inform the drug-associated risk of adverse developmental outcomes; women of childbearing potential should avoid becoming pregnant during treatment with this medicinal product and as a precautionary measure for 7 days after completing the treatment.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with this medicinal product, and until one menstrual cycle after stopping the treatment (see section 4.5).

Pregnancy

There are limited data from the use of Paxlovid in pregnant women.

Animal data with nirmatrelvir have shown developmental toxicity in the rabbit (lower foetal body weights) but not in the rat (see section 5.3).

A large number of women exposed to ritonavir during pregnancy 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).

Paxlovid is not recommended during pregnancy and in women of childbearing potential not using contraception unless the clinical condition requires treatment with this medicinal product.

Breast-feeding

Nirmatrelvir and ritonavir are excreted in breast milk (see section 5.2).

There are no available data on the effects of nirmatrelvir and 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 and as a precautionary measure for 48 hours after completing the treatment.

Fertility

There are no human data on the effect of Paxlovid (nirmatrelvir and ritonavir) or ritonavir alone on fertility. Both nirmatrelvir and ritonavir, tested separately, produced no effects on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Paxlovid is expected to have no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported during treatment with Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) were dysgeusia (4.6%), diarrhoea (3.0%), headache (1.2%) and vomiting (1.2%).

Tabulated list of adverse reactions

The safety profile of the product is based on adverse reactions reported in clinical trials and spontaneous reporting.

The adverse reactions in Table 4 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); not known (frequency cannot be estimated from the available data).

Table 4: 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, vomiting, nausea
	Uncommon	Abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Rash*
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Pruritus*
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
General disorders and administration site conditions	Rare	Malaise

* These adverse reactions are also manifestations of hypersensitivity reaction.

Description of selected adverse reactions

Patients with severe renal impairment
Based on limited data from a Phase 1, open-label study, the safety profile of Paxlovid in participants with severe renal impairment, including those requiring haemodialysis, was consistent with the safety profile observed in clinical trials.

Paediatric population
The safety of Paxlovid in paediatric patients was evaluated in a Phase 2/3, open-label, single-arm study (see section 5.1).

In the study analysis, 75 participants 6 to less than 18 years of age weighing at least 20 kg were included in the assessment of safety. The adverse reaction profile observed in this study is similar to that in the adult population.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 this medicinal product.

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 (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of the SARS-CoV-2 Mpro renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication.

Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

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 drug 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 ≤ 1.1 relative to USA-WA1/2020.

Antiviral resistance in cell cultures 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 5 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 5: SARS-CoV-2 M^{pro} amino acid substitutions selected by nirmatrelvir in cell culture (with EC_{50} fold change > 5)

S144A (2.2-5.3), E166V (25-288), P252L (5.9), T304I (1.4-5.5), 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), F140L+A173V (10.1), A173V+T304I (20.2), T21+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), L50F+F140L+L167F+T304I (54.7)

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 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 of these substitutions needs to be further understood.

Viral load rebound

Post-treatment viral nasal RNA rebounds were observed on Day 10 and/or Day 14 in a subset of Paxlovid and placebo recipients in EPIC-HR, irrespective of COVID-19 symptoms. The incidence of viral rebound in EPIC-HR occurred in both the Paxlovid treated participants and the untreated (placebo) participants, but at a numerically higher incidence in the Paxlovid arm (6.3% vs. 4.2%). Viral rebound and recurrence of COVID-19 symptoms were not associated with progression to severe disease including hospitalisation, death or emergence of resistance.

Clinical efficacy

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 kg/m^2), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study. The study excluded individuals with a history of prior COVID-19 infection or vaccination.

Participants were randomised (1:1) to receive Paxlovid (nirmatrelvir/ritonavir 300 mg/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 participants with onset of symptoms ≤ 3 days who at baseline did not receive nor were expected to receive COVID-19

therapeutic mAb treatment), the mITT1 analysis set (all treated participants with onset of symptoms ≤ 5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated participants with onset of symptoms ≤ 5 days).

A total of 2113 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 45 years with 12% of participants 65 years of age and older (3% were 75 years of age and older); 51% were male; 71% were White, 4% were Black or African American, and 15% were Asian; 41% were Hispanic or Latino; 67% of participants had onset of symptoms ≤ 3 days before initiation of study treatment; 80% had a BMI ≥ 25 kg/m^2 (36% a BMI ≥ 30 kg/m^2); 11% had diabetes mellitus; less than 1% of the study population had immune deficiency, 49% of participants were serological negative at baseline and 49% were serological positive. The mean (SD) baseline viral load was 4.71 log_{10} copies/mL (2.89); 27% of participants had a baseline viral load of > 10^7 (copies/mL); 6.0% 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 (99%), mostly clade 21J.

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 754 participants in mITT population. The estimated risk reduction was -6.5% with unadjusted 95% CI of (-9.3%, -3.7%) and a 95% CI of (-10.92%, -2.09%) when adjusting for multiplicity. The 2-sided p-value was < 0.0001 with 2-sided significance level of 0.002.

Table 6 provides results of the primary endpoint in the mITT1 analysis population for the full data set at final study completion.

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[b])

	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 Day 28, %	0	12 (1.2%)

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.
b. Data analysis set was updated after post-hoc removal of data for 133 participants due to GCP quality issues

The estimated risk reduction was -6.1% with 95% CI of (-8.2%, -4.1%) in participants dosed within 3 days of symptom onset, and -4.6% with 95% CI of (-7.4%, -1.8%) 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 1318 participants 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.

Table 7: 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=977	N=989
Serology Negative	n=475	n=497
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Estimated reduction relative to placebo (95% CI)	8 (1.7%) 1.72 (0.86, 3.40) -9.79 (-12.86, -6.72)	56 (11.3%) 11.50 (8.97, 14.68)
Serology Positive	n=490	n=479
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Estimated reduction relative to placebo (95% CI)	1 (0.2%) 0.20 (0.03, 1.44) -1.5 (-2.70, -0.25)	8 (1.7%) 1.68 (0.84, 3.33)

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, 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 between 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.

Post-hoc subgroup analysis in severely immunocompromised participants
A post-hoc subgroup analysis in severely immunocompromised participants (e.g., active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) has been performed and was derived from EPIC-IC (C4671034) study in immunocompromised participants. In participants who were severely immunocompromised, the median time to achieving NP swab SARS-CoV-2 RNA <LLOQ was numerically longer in the 5-day treatment group (28 days) compared with the 10-day (13 days) and 15-day (15 days) treatment groups. The proportion of participants with both a positive SARS-CoV-2 rapid antigen test and any self-reported targeted symptom of COVID 19 from Day 15 through Day 44 was 33.3% (6 of 18 participants), 6.3% (1 of 16 participants), and 0% (0 of 16 participants) in the 5-, 10- and 15-day nirmatrelvir/ritonavir treatment groups, respectively. The incidence of viral RNA rebound observed in the severely immunocompromised participants was 25% (5 of 20 participants), 0% (0 of 17 participants) and 5% (1 of 20 participants) in the 5-, 10-, and 15-day Paxlovid treatment groups, respectively.

Paediatric population

Paxlovid was evaluated in a Phase 2/3, open-label, single-arm study (EPIC-PEDS, C4671026) investigating the safety, tolerability, pharmacokinetics, and efficacy in non-hospitalised symptomatic paediatric participants with confirmed COVID-19 who are at risk of progression to severe disease. Data are available from 75 participants 6 to less than 18 years of age weighing at least 20 kg who received Paxlovid (nirmatrelvir/ritonavir 150 mg/100 mg or 300 mg/100 mg) orally every 12 hours for 5 days. The most frequently reported risk factors at baseline for progression to severe disease were obesity (49%) and chronic lung disease (40%).

Efficacy in paediatric patients is based on matching exposure to adult COVID-19 patients.

The European Medicines Agency has deferred the obligation to submit the results of studies with Paxlovid in one or more subsets of the paediatric population in treatment of COVID-19 (see section 4.2 for information on paediatric use).

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 enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir.

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 C_{max} and AUC_{inf} at steady-state was 2.21 µg/mL and 23.01 µg*hr/mL, respectively. The median time to C_{max} (T_{max}) was 3.00 hrs. The arithmetic mean terminal elimination half-life was 6.1 hours.

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir C_{max} and AUC_{inf} was 0.36 µg/mL and 3.60 µg*hr/mL, respectively. The median time to C_{max} (T_{max}) was 3.98 hrs. The arithmetic mean terminal elimination half-life was 6.1 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 cytochrome P450 (CYP) 3A4. However, administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In plasma, the only medicinal product-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 CYP3A is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of oxidation metabolite M–2.

Elimination

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact medicinal product. 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

Paediatric population
The pharmacokinetics of nirmatrelvir following nirmatrelvir/ritonavir 150 mg/100 mg or 300 mg/100 mg dosing twice daily have been evaluated in 68 paediatric participants 6 years of age and older weighing at least 20 kg (see section 5.1).

Population pharmacokinetic analyses and model-based simulation demonstrated that the pharmacokinetics of nirmatrelvir/ritonavir in paediatric participants 6 years of age and older weighing at least 20 kg were similar to those in adult participants after accounting for weight differences (Table 8), with C_{max}, AUC_{tau}, and C_{min} values of 1.2, 1.4, and 1.7-fold higher, respectively. The recommended paediatric dosing regimens in participants 6 years of age and older weighing at least 20 kg result in no clinically relevant differences in systemic exposure to those in adults receiving nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days (see section 4.2).

Table 8: Pharmacokinetic parameters of nirmatrelvir on Day 5 estimated using population PK modeling following administration of recommended paediatric nirmatrelvir/ritonavir dosing regimens[b]

Patient population	Paediatric dose	C_{max} (µg/mL)[a]	AUC_{tau} (µg*hr/mL)[a,c]	C_{min} (µg/mL)[a]
Paediatric participants ≥6 years of age weighing ≥40 kg	300 mg nirmatrelvir/100 mg ritonavir twice daily for 5 days	4.31 (2.88, 6.40)	36.3 (22.5, 58.3)	1.62 (0.71, 3.48)
Paediatric participants ≥6 years of age weighing ≥20 to <40 kg	150 mg nirmatrelvir/100 mg ritonavir twice daily for 5 days	4.11 (2.76, 6.15)	34.1 (21.0, 55.3)	1.47 (0.61, 3.19)

Abbreviations: C_{max}=predicted maximal concentration; C_{min}=predicted minimal concentration (C_{trough}).
a. Data presented as geometric mean (10^{th} and 90^{th} percentile).
b. Data presented were generated using a population PK analysis model (adult Phase 1 + paediatric) simulation of 10,000 virtual subjects in each group.
c. AUC_{tau}=predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice daily dosing.

There is insufficient information to assess the exposure of Paxlovid in paediatric patients weighing less than 20 kg.

Age and gender
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.

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

Severe renal impairment including those requiring haemodialysis
The pharmacokinetics of nirmatrelvir in adult participants with mild-to-moderate COVID-19 and severe renal impairment (eGFR< 30 mL/min) either requiring haemodialysis (n=12) or not requiring haemodialysis (n=2) were evaluated after administration of 300 mg/100 mg nirmatrelvir/ritonavir once on Day 1 followed by 150 mg/100 mg nirmatrelvir/ritonavir once daily on Days 2-5 for a total of 5 doses.

During a 4-hour haemodialysis session, approximately 6.9% of nirmatrelvir dose was cleared through dialysis. Haemodialysis clearance was 1.83 L/h.

Population pharmacokinetic model-based simulations showed that administration of 300 mg/100 mg nirmatrelvir/ritonavir once on Day 1 followed by 150 mg/100 mg nirmatrelvir/ritonavir once daily on Days 2-5 in adult participants with severe renal impairment resulted in comparable exposures on Day 1 and at steady-state (AUC_{0-24} and C_{max}) to those observed in adult participants with normal renal function receiving 300 mg/100 mg nirmatrelvir/ritonavir twice daily for 5 days.

Based on the results of population PK analysis model-based simulation, dose reduction in paediatric patients 6 years of age and older weighing at least 40 kg with renal impairment should parallel that recommended for adults with the same degree of renal impairment.

Dose in paediatric patients with renal impairment weighing less than 40 kg has not been determined.

Hepatic impairment
Compared to healthy controls with no hepatic impairment, the pharmacokinetics of nirmatrelvir in participants with moderate hepatic impairment was not significantly different. Adjusted geometric mean ratio (90% CI) of AUC_{inf} and C_{max} of nirmatrelvir comparing moderate hepatic impairment (test) to normal hepatic function (reference) was 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.

Breast-feeding mothers
Following 3 doses of nirmatrelvir/ritonavir 300 mg/100 mg administered twice daily in 8 healthy lactating women, under high-fat high-calorie fed conditions, both nirmatrelvir and ritonavir were excreted into breast milk. The estimated milk to plasma ratios for C_{max} and AUC were 0.27 and 0.26, respectively for nirmatrelvir and 0.06 and 0.07, respectively for ritonavir.

<u>Interaction studies conducted with nirmatrelvir/ritonavir</u>

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

Nirmatrelvir does not reversibly inhibit CYP2B6, 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, MATE1, MATE2K, OAT1, OAT3, OATP1B3, OCT1 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1 and OATP1B1 at clinically relevant concentrations.

The effect on the pharmacokinetics of nirmatrelvir/ritonavir was assessed with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer). The test/reference ratios of the adjusted geometric means for nirmatrelvir AUC_{inf} and C_{max} were 44.50% and 56.82%, respectively, following nirmatrelvir/ritonavir 300 mg/100 mg coadministration with multiple oral doses of carbamazepine. The test/reference ratios of the adjusted geometric means for nirmatrelvir AUC_{tau} and C_{max} were

138.82% and 118.57%, respectively, when nirmatrelvir/ritonavir was coadministered with multiple doses of itraconazole as compared to nirmatrelvir/ritonavir administered alone.

The effect of nirmatrelvir/ritonavir on other drugs was assessed with midazolam (CYP3A substrate), dabigatran (P-gp substrate), and rosuvastatin (OATP1B1 substrate). The test/reference ratios of the adjusted geometric means for midazolam AUC_{inf} and C_{max} were 1430.02% and 368.33%, respectively, when midazolam was coadministered with multiple doses of nirmatrelvir/ritonavir compared to midazolam administered alone. The test/reference ratios of the adjusted geometric means for dabigatran AUC_{inf} and C_{max} were 194.47% and 233.06%, respectively, following dabigatran administration with multiple doses of nirmatrelvir/ritonavir as compared to administration of dabigatran alone. The test/reference ratios of the adjusted geometric means for rosuvastatin AUC_{inf} and C_{max} were 131.18% and 212.44%, respectively, following rosuvastatin administration with multiple doses of nirmatrelvir/ritonavir as compared to administration of rosuvastatin alone.

5.3 Preclinical safety data

No nonclinical safety studies have been conducted with nirmatrelvir in combination with ritonavir.

Nirmatrelvir

Studies of repeated dose toxicity and genotoxicity revealed no risk due to nirmatrelvir. No adverse effects were observed in fertility, embryo-foetal development, or pre- and postnatal development studies in rats. A study in pregnant rabbits showed an adverse decrease in foetal body weight, in the absence of significant maternal toxicity. Systemic exposure (AUC_{24}) in rabbits at the maximum dose without adverse effect in foetal body weight was estimated to be approximately 3 times higher than exposure in humans at recommended therapeutic dose of Paxlovid.

No carcinogenicity studies have been conducted with nirmatrelvir.

Ritonavir

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.

Genotoxicity studies revealed no risk due to ritonavir. Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumourigenic potential specific for these species, but are regarded as of no relevance for humans. Ritonavir produced no effects on fertility in rats. Developmental toxicity observed in rats (embryo-lethality, decreased foetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at a maternally toxic dose. Developmental toxicity in rabbits (embryo-lethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nirmatrelvir film-coated tablets

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate

Film coat
Hydroxypropyl methylcellulose (E464)
Titanium dioxide (E171)
Macrogol/polyethylene glycol (E1521)
Iron oxide red (E172)

Ritonavir film-coated tablets

Tablet core
Copovidone
Sorbitan laurate
Silica, colloidal anhydrous (E551)
Calcium hydrogen phosphate
Sodium stearyl fumarate

Film coat
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol/polyethylene glycol (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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Al/PVC foil blister cards.

Pack size of 5 blister cards each containing 4 nirmatrelvir tablets and 2 ritonavir tablets for morning and evening dose (total of 30 tablets).

Pack size of one blister card containing 6 nirmatrelvir tablets and 5 ritonavir tablets for once daily dose (total of 11 tablets).

Pack size of 5 blister cards each containing 2 nirmatrelvir tablets and 2 ritonavir tablets for morning and evening dose (total of 20 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1625/001
EU/1/22/1625/002
EU/1/22/1625/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 January 2022
Date of latest renewal: 28 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

Pfizer Italia S.r.L.
Localita Marino del Tronto
63100 Ascoli, Piceno
Italy

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell
Newbridge
County Kildare
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID 150 mg + 100 mg film-coated tablets
nirmatrelvir + ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pink film-coated tablet contains 150 mg of nirmatrelvir
Each white film-coated tablet contains 100 mg of ritonavir

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets (20 nirmatrelvir tablets + 10 ritonavir tablets)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Scan QR code for product information in the national language.
URL: www.covid19oralrx.com/en

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1625/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

paxlovid

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID
nirmatrelvir 150 mg tablet
ritonavir 100 mg tablet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID 150 mg + 100 mg film-coated tablets
nirmatrelvir + ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pink film-coated tablet contains 150 mg of nirmatrelvir
Each white film-coated tablet contains 100 mg of ritonavir

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

11 film-coated tablets (6 nirmatrelvir tablets + 5 ritonavir tablets)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Scan QR code for product information in the national language.
URL: www.covid19oralrx.com/en

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1625/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

paxlovid

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID
nirmatrelvir 150 mg tablet
ritonavir 100 mg tablet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Day 1
Your first day's dose. Take these 3 tablets together.

Days 2 to 5
Take these 2 tablets together.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID 150 mg + 100 mg film-coated tablets
nirmatrelvir + ritonavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pink film-coated tablet contains 150 mg of nirmatrelvir
Each white film-coated tablet contains 100 mg of ritonavir

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

20 film-coated tablets (10 nirmatrelvir tablets + 10 ritonavir tablets)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Scan QR code for product information in the national language.
URL: https://www.covid19oralrx.com/en

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1625/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

paxlovid

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

PAXLOVID
nirmatrelvir 150 mg tablet
ritonavir 100 mg tablet

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Paxlovid 150 mg + 100 mg film-coated tablets
nirmatrelvir + ritonavir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Paxlovid is and what it is used for

Paxlovid contains two active substances nirmatrelvir and ritonavir in two different tablets. Paxlovid is an antiviral medicine used for treating adults and children and adolescents 6 years to less than 18 years of age weighing at least 20 kg with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe disease.

COVID-19 is caused by a virus called a coronavirus. This medicine stops the virus multiplying in cells and this stops the virus multiplying in the body. This can help your body to overcome the virus infection, and may prevent you from developing severe illness.

You must talk to a doctor if you do not feel better or if you feel worse after 5 days.

2. What you need to know before you take Paxlovid

Do not take Paxlovid
- if you are allergic to nirmatrelvir, ritonavir or any of the other ingredients of this medicine (listed in section 6).
- if you are taking any of the following medicines. Taking Paxlovid with these medicines may cause serious or life-threatening side effects or affect how Paxlovid works:
  - Alfuzosin (used to treat symptoms of an enlarged prostate)
  - Ranolazine (used to treat chronic chest pain [angina])
  - Dronedarone, propafenone, quinidine (used to treat heart conditions and correct irregular heartbeats)
  - Rifampicin, rifapentine (used to treat bacterial infections)
  - Apalutamide, enzalutamide, neratinib, venetoclax (used to treat cancer)
  - Carbamazepine, phenobarbital, phenytoin, primidone (used to prevent and control seizures)

- Colchicine (used to treat gout)
- Terfenadine (used to treat allergies)
- Cariprazine and lurasidone (used to treat schizophrenia)
- Pimozide, quetiapine (used to treat schizophrenia, bipolar disorder, severe depression and abnormal thoughts or feelings)
- Silodosin (used to treat enlarged prostate gland)
- Eplerenone and ivabradine (used to treat heart and/or blood vessel problems)
- Dihydroergotamine and ergotamine (used to treat migraine headaches)
- Ergonovine and methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion)
- Cisapride (used to relieve certain stomach problems)
- St. John's wort (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- Voclosporin (used to treat immune disorders)
- Lovastatin, simvastatin, lomitapide (used to lower blood cholesterol)
- Eletriptan (used to treat migraine headaches)
- Lumacaftor/ivacaftor (used for cystic fibrosis)
- Finerenone (used to treat chronic kidney disease associated with Type 2 diabetes)
- Naloxegol (used to treat opioid-induced constipation)
- Avanafil, vardenafil (used to treat erectile dysfunction [also known as impotence])
- Sildenafil, tadalafil (used to treat erectile dysfunction [also known as impotence] or pulmonary arterial hypertension [high blood pressure in the pulmonary artery])
- Clorazepate, diazepam, estazolam, flurazepam, triazolam, midazolam taken orally (used to relieve anxiety and/or trouble sleeping)
- Tolvaptan used to treat hyponatremia (low sodium levels in the blood)

Warnings and precautions

Allergic reactions
Allergic reactions, including severe allergic reactions (known as 'anaphylaxis') and serious skin reactions (known as 'toxic epidermal necrolysis' and 'Stevens-Johnson syndrome'), can happen in people taking this medicine, even after only 1 dose. Stop taking this medicine and call your doctor right away if you get any of the following symptoms of an allergic reaction:
- trouble swallowing or breathing
- swelling of the tongue, mouth, and face
- throat tightness
- hoarseness
- itching
- skin rash
- red and painful skin
- blisters and peeling skin
- blisters or sores in your mouth or lips

Liver disease
Tell your doctor if you have or have had a liver disease. Liver enzyme abnormalities, hepatitis and jaundice have occurred in patients receiving ritonavir.

Kidney disease
Tell your doctor if you have or have had a kidney disease.

High blood pressure
Tell your doctor if you have high blood pressure. Your doctor may need to check your blood pressure before taking this medicine and while you are taking this medicine. There have been reports of high blood pressure in people taking this medicine, particularly in older individuals.

Risk of HIV-1 resistance development
If you have untreated or uncontrolled HIV infection, Paxlovid may lead to some HIV medicines not working as well in the future.

Children and adolescents
Do not give this medicine to children under 6 years or children and adolescents 6 years to less than 18 years of age weighing less than 20 kg because this medicine has not been studied in this group.

Other medicines and Paxlovid
There are other medicines that may not be taken together with Paxlovid. Tell your doctor(s) or pharmacist if you are taking, have recently taken or might take any other medicines:

- medicines used to treat cancer, such as afatinib, abemaciclib, ceritinib, dasatinib, encorafenib, fostamatinib, ibrutinib, ivosidenib, nilotinib, vinblastine and vincristine
- medicines used to thin the blood (anticoagulants), such as warfarin, rivaroxaban, dabigatran and apixaban
- medicines used to treat convulsions, such as divalproex, lamotrigine and clonazepam
- medicines used for smoking cessation, such as bupropion
- medicines used to treat allergies, such as fexofenadine and loratadine
- medicines used to treat fungal infections (antifungals), such as itraconazole and voriconazole
- medicines used to treat parasitic infections, such as albendazole
- medicines used to treat Cushing's syndrome—when the body produces an excess of cortisol—such as ketoconazole tablets
- medicines used to treat HIV infection, such as efavirenz, maraviroc, raltegravir, zidovudine and bictegravir/emtricitabine/tenofovir
- medicines used to treat infections (e.g., antibiotics and antimycobacterials), such as atovaquone, clarithromycin, erythromycin, fusidic acid (taken orally or administered by IV route), bedaquiline, rifabutin, delamanid and sulfamethoxazole/trimethoprim
- medicines used to treat schizophrenia and abnormal thoughts or feelings, such as clozapine
- medicines used to treat mental or mood disorders, such as haloperidol, risperidone and thioridazine
- medicines used to treat high blood pressure in the blood vessels that supply the lungs, such as bosentan and riociguat
- medicines used to treat high blood pressure (hypertension), such as amlodipine, diltiazem, felodipine, lercanidipine, nicardipine, nifedipine and verapamil
- medicines used to treat heart and/or blood vessel problems, such as aliskiren, ticagrelor, cilostazol and clopidogrel
- medicines used to treat heart conditions and correct irregular heartbeats, such as digoxin, amiodarone, flecainide and disopyramide
- medicines to treat cystic fibrosis, such as ivacaftor, elexacaftor/tezacaftor/ivacaftor and tezacaftor/ivacaftor
- medicines used to treat diabetes such as saxagliptin
- medicines used to treat hepatitis C virus infection, such as glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir
- medicines used to lower blood cholesterol, such as atorvastatin, fluvastatin, pravastatin and rosuvastatin
- medicines used to treat migraine headaches, such as rimegepant
- medicines used to treat urinary incontinence, such as darifenacin and solifenacine
- medicines used to treat mental health problems, such as aripiprazole and brexpiprazole
- medicines used to suppress your immune system, such as cyclosporine, everolimus, sirolimus and tacrolimus
- medicines used to treat autoimmune disorders including rheumatoid arthritis, psoriatic arthritis or ulcerative colitis, such as tofacitinib and upadacitinib
- medicines used to treat severe pain, such as morphine, fentanyl, oxycodone, methadone, buprenorphine, other morphine-like medicines, pethidine and piroxicam
- medicines used as sedatives, hypnotics, and sleeping agent, such as alprazolam, buspirone and zolpidem

- medicines used to treat attention deficit disorder or a sleep disorder called narcolepsy, such as amphetamines
- steroids including corticosteroids used to treat inflammation, such as budesonide, dexamethasone, fluticasone, prednisolone and triamcinolone
- medicines used to treat asthma and other lung-related problems such as chronic obstructive pulmonary disease [COPD], such as salmeterol and theophylline
- medicines used to treat depression, such as amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine and sertraline
- medicines used as thyroid replacement therapy, such as levothyroxine
- medicine used to treat enlarged prostate, such as tamsulosin
- any of the following other specific medicines:
    - oral or patch contraceptive containing ethinyl estradiol used to prevent pregnancy
    - midazolam administered by injection (used for sedation [an awake but very relaxed state of calm or drowsiness during a medical test or procedure] or anaesthesia)

Many medicines interact with Paxlovid. **Keep a list of your medicines to show your doctor(s) and pharmacist.** Do not start taking a new medicine without telling your doctor(s). Your doctor(s) can tell you if it is safe to take Paxlovid with other medicines.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

There is not enough information to be sure that Paxlovid is safe for use in pregnancy. If you are pregnant, it is not recommended to use this medicine unless your clinical condition requires this treatment. It is recommended that you refrain from sexual activity or use contraception while taking this medicine and for 7 days after completing the treatment as a precaution. If you are taking hormonal contraception, as this medicine may reduce the effectiveness of this medicine, it is recommended that a condom or other non hormonal method of contraception is used. Your doctor will advise you on the duration of this required adjustment of your contraceptive measures.

A small amount of Paxlovid passes into breast milk. You should not breast-feed your baby while taking this medicine and for 48 hours after completing the treatment as a precaution.

Driving and using machines
Paxlovid is expected to have no influence on the ability to drive and use machines.

Paxlovid contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take Paxlovid

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Paxlovid consists of 2 medicines: nirmatrelvir and ritonavir.

A course of treatment lasts 5 days.

Swallow the tablets whole. Do not chew, break or crush the tablets. This medicine can be taken with or without meals.

Recommended dose

Adults

The recommended dose is **2** pink nirmatrelvir tablets with **1** white ritonavir tablet by mouth every 12 hours (in the morning and in the evening).

Children and adolescents 6 years to less than 18 years of age

- Weight at least 20 kg to less than 40 kg:
The recommended dose is **1** pink nirmatrelvir tablet with **1** white ritonavir tablet by mouth every 12 hours (in the morning and in the evening).

- Weight at least 40 kg:
The recommended dose is **2** pink nirmatrelvir tablets with **1** white ritonavir tablet by mouth every 12 hours (in the morning and in the evening).

If you or your child have/has a kidney disease, the dose of Paxlovid should be reduced. Please talk to your healthcare provider for an appropriate dose of PAXLOVID.

Severe kidney disease
If you have SEVERE kidney disease, the recommended dose is **2** pink nirmatrelvir tablets with **1** white ritonavir tablet by mouth once **on Day 1**, and then **1** pink nirmatrelvir tablet with **1** white ritonavir tablet once daily **on Days 2 to 5**.

If you take more Paxlovid than you should
If you take too much of this medicine, call your healthcare provider or go to the nearest hospital emergency room right away.

If you forget to take Paxlovid
If you miss a dose of this medicine within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses at the same time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Paxlovid
Even if you feel better, do not stop taking this medicine without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- Diarrhoea
- Vomiting
- Nausea
- Altered sense of taste (such as metallic, bitter taste)
- Headache

Uncommon: may affect up to 1 in 100 people
- Allergic reactions
- High blood pressure
- Abdominal pain
- Muscle pain
- Skin rash (also reported as part of allergic reaction)

Rare: may affect up to 1 in 1000 people
- Severe allergic reaction known as 'anaphylaxis' (such as swelling of tongue, mouth and face, trouble swallowing or breathing, throat tightness, or hoarseness)
- Serious skin reactions known as 'toxic epidermal necrolysis' and 'Stevens-Johnson syndrome' (such as red and painful skin, blisters and peeling skin, blisters or sores in your mouth or lips)
- Malaise
- Itching (also reported as part of allergic reaction)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Paxlovid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Paxlovid contains
- The active substances in this medicine are nirmatrelvir and ritonavir.
  - Each pink film-coated nirmatrelvir tablet contains 150 mg of nirmatrelvir.
  - Each white film-coated ritonavir tablet contains 100 mg of ritonavir.
- The other ingredients in the nirmatrelvir tablet are microcrystalline cellulose, lactose monohydrate (see section 2, 'Paxlovid contains lactose'), croscarmellose sodium, colloidal silicon dioxide and sodium stearyl fumarate (see section 2, 'Paxlovid contains sodium'). The film-coating contains hydroxypropyl methylcellulose, titanium dioxide, macrogol/polyethylene glycol and iron oxide red.
- The other ingredients in the ritonavir tablet are copovidone, sorbitan laurate, colloidal anhydrous silica, calcium hydrogen phosphate, sodium stearyl fumarate. The film-coating contains hypromellose, titanium dioxide, macrogol/polyethylene glycol, hydroxypropyl cellulose, talc, colloidal anhydrous silica and polysorbate 80.

What Paxlovid looks like and contents of the pack

Nirmatrelvir 150 mg film-coated tablets are pink, oval-shaped and debossed with 'PFE' on one side and '3CL' on the other side.

Ritonavir 100 mg film-coated tablets are white to off white, capsule-shaped, and debossed with 'H' on one side and 'R9' on the other side.

Paxlovid film-coated tablets are available in 5 daily-dose blister cards with a total of 30 tablets or 20 tablets packaged in a carton.

In the 30-tablet pack, each daily blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening (sun and moon symbols).

In the 20-tablet pack, each daily blister card contains 2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening (sun and moon symbols).

Paxlovid film-coated tablets are also available in a 5-day blister card with a total of 11 tablets packaged in a carton. The 5-day blister card contains 6 nirmatrelvir tablets (150 mg each) and 5 ritonavir tablets (100 mg each) and indicates which tablets need to be taken once daily for 5 days.

Not all pack sizes may be marketed.

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This leaflet was last revised in

Scan the code with a mobile device to get the package leaflet in different languages.

URL: www.covid19oralrx.com/en

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

ANNEX IV

CONCLUSIONS ON THE REQUEST FOR ONE-YEAR MARKETING PROTECTION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **one-year marketing protection**

The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.