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 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

The recommended dosage 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. 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 Paxlovid.

If the patient misses a dose of Paxlovid 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 (eGFR ≥ 60 to < 90 mL/min). In patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min), the dose of Paxlovid should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg every 12 hours for 5 days to avoid over-exposure (this dose adjustment has not been clinically tested). Paxlovid should not be used in patients with severe renal impairment [eGFR < 30 mL/min, including patients with End Stage Renal Disease (ESRD) under haemodialysis] (see sections 4.4 and 5.2).

Special attention for patients with moderate renal impairment
The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose.
Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours.

Hepatic impairment
No dose adjustment of Paxlovid 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 hepatic impairment (see sections 4.4 and 5.2).

Concomitant therapy with ritonavir- or cobicistat-containing regimen
No dose adjustment of Paxlovid 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 patients below 18 years of age have not been established. No data are available.

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.

Paxlovid can be taken with or without food. 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 concentrations are associated with serious and/or life-threatening reactions.

- $Alpha_1$-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine

- Antibiotics: fusidic acid
- Anticancer drugs: neratinib, venetoclax
- Anti-gout: colchicine
- Antihistamines: terfenadine
- Antipsychotics/neuroleptics: clozapine, 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
- 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
- Anticancer drugs: apalutamide
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- 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 dosage 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).

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

See Table 1 for medicinal products that are contraindicated for concomitant use with nirmatrelvir/ritonavir 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 and other hypersensitivity reactions have been reported with Paxlovid (see section 4.8). Cases of Toxic Epidermal Necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of Paxlovid (refer to Norvir Summary of Product Characteristics). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care.

Severe renal impairment

No clinical data are available in patients with severe renal impairment (including patients with ESRD). Based on pharmacokinetic data (see section 5.2), the use of Paxlovid in patients with severe renal impairment could lead to over-exposure with potential toxicity. No recommendation in terms of dose adjustment could be elaborated at this stage pending dedicated investigation. Therefore, Paxlovid should not be used in patients with severe renal impairment (eGFR < 30 mL/min, including patients with ESRD under haemodialysis).

Severe hepatic impairment

No pharmacokinetic and clinical data are available in patients with severe hepatic impairment. Therefore, Paxlovid 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 Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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 1). Coadministration of other CYP3A4 substrates that may lead to potentially significant interaction (see Table 1) 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, 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, MATE1, OCT1 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 1 are a guide and not considered a comprehensive list of all possible medicinal products that are contraindicated or may interact with nirmatrelvir/ritonavir.

Table 1: 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).
Amphetamine derivatives	↑Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		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	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.
	↓Methadone (36%, 38%)	Increased methadone dose may be necessary when coadministered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
	↓Morphine	Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir dosed as a pharmacokinetic enhancer.
	↑Pethidine	Coadministration could result in increased or prolonged opioid effects. If concomitant use is necessary, consider dosage 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).

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Antiarrhythmics	↑Amiodarone, ↑Dronedarone, ↑Flecainide, ↑Propafenone, ↑Quinidine	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and is therefore contraindicated (see section 4.3).
	↑Digoxin	This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer. Digoxin drug concentration is expected to increase. Monitor digoxin levels if possible and digoxin safety and efficacy.
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 dosage adjustment recommendations. Monitor for ADRs related to abemaciclib.
	↑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

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		dosage 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	Serum concentrations of encorafenib may be increased when coadministered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Coadministration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.
	↑Fostamatinib	Coadministration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Refer to the fostamatinib 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

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions).
Anticoagulants	↑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. Refer to the dabigatran product label for further information.
	↑Rivaroxaban (153%, 53%)	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of 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	Carbamazepine decreases AUC and C_{max} of nirmatrelvir by 55% and 43%, respectively. Phenobarbital and phenytoin 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 and phenytoin with Paxlovid is contraindicated (see section 4.3).
	↓Divalproex, Lamotrigine, Phenytoin	Ritonavir dosed as a pharmacokinetic enhancer induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are coadministered with ritonavir. Phenytoin may decrease serum levels of ritonavir.

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
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 dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).
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.
Antihistamines	↑Fexofenadine ↑Loratadine ↑Terfenadine	Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. 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. 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	↑Efavirenz (21%)	A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		enzymes) have been observed when efavirenz is coadministered with ritonavir.
	↑Maraviroc (161%, 28%)	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the 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

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if coadministration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full 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	Ritonavir coadministration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).
	↑Rifabutin (4-fold, 2.5-fold), ↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold)	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when coadministered with ritonavir as a pharmacokinetic enhancer.
	Rifampicin	Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of nirmatrelvir/ritonavir and potential loss of virologic response. Concomitant use of rifampicin with Paxlovid is contraindicated (see section 4.3).
	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 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Antipsychotics	↑Clozapine, ↑Pimozide	Ritonavir coadministration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see section 4.3).
	↑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).
	↑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. Therefore, concomitant use is not recommended.
Calcium channel antagonist	↑Amlodipine, ↑Diltiazem, ↑Nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when amlodipine, diltiazem or nifedipine are concomitantly administered with ritonavir.
	↑Lercanidipine	Coadministration of lercanidipine and Paxlovid should be avoided.
Cardiovascular agents	↑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

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		bradycardia or conduction disturbances (see section 4.3).
Endothelin antagonists	↑Bosentan ↑Riociguat	Coadministration of bosentan and ritonavir may increase steady-state bosentan maximum concentrations (C_{max}) and AUC. 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	↑Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see section 4.3). Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.
Hormonal contraceptive	↓Ethinyl Estradiol (40%, 32%)	Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives.
Immunosuppressants	↑Voclosporin	Coadministration is contraindicated due to potential for acute and/or chronic nephrotoxicity (see section 4.3).
Immunosuppressants	↑Cyclosporine, ↑Everolimus, ↑Sirolimus, ↑Tacrolimus	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 serum concentrations, to reduce the dose of the immunosuppressant so that 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.
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).
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

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		information for lomitapide) (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 dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
	↑Buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.
	↑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. Dosage adjustment for midazolam should

Table 1: Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑Triazolam (> 20-fold, 87%)	be considered, especially if more than a single dose of midazolam is administered. 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. 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 dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.

Table 1: Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There are no 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 Paxlovid and as a precautionary measure for 7 days after completing Paxlovid.

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

Pregnancy

There are no data from the use of Paxlovid in pregnant women.

There was no nirmatrelvir-related effect on foetal morphology or embryo-foetal viability at any dose tested in rat or rabbit embryo-foetal developmental toxicity studies although lower foetal body weights were observed in rabbit (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 Paxlovid.

Breast-feeding

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

It is unknown whether nirmatrelvir is present in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or 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 7 days after completing Paxlovid.

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) every 12 hours for 5 days and during 34 days after the first dose were dysgeusia (5.6%), diarrhoea (3.1%), headache (1.4%) and vomiting (1.1%).

Tabulated summary of adverse reactions

The adverse reactions in Table 2 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (frequency cannot be estimated from the available data).

Table 2: Adverse reactions with Paxlovid

System organ class	Frequency category	Adverse reactions
Immune system disorders	Uncommon	Hypersensitivity including pruritus and rash
	Rare	Anaphylaxis
Nervous system disorders	Common	Dysgeusia, headache
Gastrointestinal disorders	Common	Diarrhoea, vomiting, nausea
	Uncommon	Abdominal pain
General disorders and administration site conditions	Rare	Malaise

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 Paxlovid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (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 dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure. Nirmatrelvir had cell culture antiviral activity (with EC_{50} values in the low nanomolar range ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3.3-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

Resistance
No information on antiviral resistance is currently available to nirmatrelvir with SARS-CoV-2. Studies to evaluate selection of resistance to nirmatrelvir with SARS-CoV-2 in cell culture and clinical studies have not been completed. Only *in vitro* resistance selection study with murine hepatitis virus (MHV)-Mpro is available. It showed a 4.4- to 5-fold decrease in nirmatrelvir susceptibility against mutant viruses with 5 mutations (Pro55Leu, Ser144Ala, Thr129Met, Thr50Lys, Pro15Ala) in the MHV-Mpro following 10 passages in cell culture. The relevance for this to SARS-CoV-2 is not known.

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

A total of 2,246 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 46 years with 13% of participants 65 years of age and older (3% were 75 years of age and older); 51% were male; 72% were White, 5% were Black, and 14% were Asian; 45% were Hispanic or Latino; 66% of participants had onset of symptoms ≤ 3 days before initiation of study treatment; 81% had a BMI ≥ 25 kg/m^2 (37% a BMI ≥ 30 kg/m^2); 12% had diabetes mellitus; less than 1% of the study population had immune deficiency, 47% of participants were serological negative at baseline and 51% were serological positive. The mean (SD) baseline viral load was 4.63 log_{10} copies/mL (2.87); 26% of participants had a baseline viral load of > 10^7 (copies/mL); 6.2% of participants either received or were expected to receive COVID-19 therapeutic mAb treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), mostly clade 21J (based on interim analysis).

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

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with unadjusted 95% CI of (-9.0%, -3.6%) and a 95% CI of (-10.61%, -2.02%) when adjusting for multiplicity. The 2-sided p-value was <0.0001 with 2-sided significance level of 0.002.

Table 3 provides results of the primary endpoint in the mITT1 analysis population for the full data set at final study completion.

Table 3: Efficacy results in non-hospitalised adults with COVID-19 dosed within 5 days of symptom onset who did not receive COVID-19 monoclonal antibody treatment at baseline (mITT1 analysis set)

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

Abbreviations: CI=confidence interval.

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

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

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

Table 4: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 analysis set

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

Abbreviations: CI=confidence interval; mITT=modified intent-to-treat. All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 5 days after COVID-19 symptom onset.
Seropositivity was defined if results were positive in a serological immunoassay specific for host antibodies to either S or N viral proteins.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on normal approximation of the data are presented.
a. COVID-19 related hospitalisation or death from any cause.

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

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

Paediatric population

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.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations 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 modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir coadministered with ritonavir tablets.

Distribution

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

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

Biotransformation

In vitro studies assessing nirmatrelvir without concomitant ritonavir suggest that nirmatrelvir is primarily metabolised by 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

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

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

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

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

Interaction studies conducted with nirmatrelvir/ritonavir

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

Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 *in vitro* at clinically relevant concentrations. *In vitro* study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. The clinical relevance is unknown. Based on *in vitro* data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.

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 proteinurea 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 dosage. Developmental toxicity in rabbits (embryo-lethality, decreased litter size and decreased foetal weights) occurred at a maternally toxic dosage.

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)
Polyethylene glycol (E1521)
Iron oxide red (E172)

Ritonavir film-coated tablets

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

Film coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Hydroxypropyl cellulose (E463)
Talc (E553b)
Silica, colloidal anhydrous (E551)
Polysorbate 80 (E433)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Al/PVC foil blister cards of 30 tablets.

Paxlovid is packaged in cartons containing 5 daily-dose blister cards of 30 tablets.

Each daily blister card contains 4 nirmatrelvir tablets and 2 ritonavir tablets for morning and evening dose.

6.6 Special precautions for disposal

No special requirements 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

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 http://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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

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

Pfizer Ireland Pharmaceuticals
Little Connell
Newbridge
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.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance nirmatrelvir for commercial supply.	30 June 2022
In order to ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance nirmatrelvir for the impurities including chiral impurities and the active substance should be fully established.	30 June 2022
In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance nirmatrelvir should be provided.	30 June 2022

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: https://pfi.sr/c19oralrx

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

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 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. Paxlovid 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.

If your symptoms worsen or do not improve after 5 days, talk to your doctor.

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 Paxlovid (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])
  - Amiodarone, dronedarone, flecainide, propafenone, quinidine (used to treat heart conditions and correct irregular heartbeats)
  - Fusidic acid, rifampicin (used to treat bacterial infections)
  - Apalutamide, neratinib, venetoclax (used to treat cancer)
  - Carbamazepine, phenobarbital, phenytoin (used to prevent and control seizures)
  - Colchicine (used to treat gout)
  - Terfenadine (used to treat allergies)

- Lurasidone (used to treat schizophrenia)
- Pimozide, clozapine, 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)
- 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'), can happen in people taking Paxlovid, even after only 1 dose. Stop taking Paxlovid 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

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.

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 Paxlovid to children and adolescents under 18 years because Paxlovid has not been studied in children and adolescents.

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

- medicines used to treat cancer, such as afatinib, abemaciclib, apalutamide, ceritinib, dasatinib, encorafenib, fostamatinib, ibrutinib, nilotinib, vinblastine and vincristine
- medicines used to thin the blood (anticoagulants), such as warfarin, rivaroxaban and dabigatran
- medicines used to treat convulsions, such as divalproex, lamotrigine

- 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 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 and zidovudine
- medicines used to treat infections (e.g., antibiotics and antimycobacterials), such as atovaquone, clarithromycin, erythromycin, bedaquiline, rifabutin, delamanid and sulfamethoxazole/trimethoprim
- 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, lercanidipine and nifedipine
- medicines used to treat heart conditions and correct irregular heartbeats, such as digoxin
- medicines used to treat hepatitis C virus infection, such as glecaprevir/pibrentasvir
- medicines used to lower blood cholesterol, such as atorvastatin, fluvastatin, pravastatin and rosuvastatin
- medicines used to suppress your immune system, such as cyclosporine, everolimus, sirolimus and tacrolimus
- medicines used to treat severe pain, such as morphine, fentanyl, methadone, buprenorphine, other morphine-like medicines, and piroxicam
- medicines used as sedatives, hypnotics, and sleeping agent, such as alprazolam, buspirone and zolpidem
- steroids including corticosteroids used to treat inflammation, such as betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, prednisolone, prednisone 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
- 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 and pharmacist.** Do not start taking a new medicine without telling your doctor. Your doctor 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 Paxlovid unless your clinical condition requires this treatment. It is recommended that you refrain from sexual activity or use contraception while taking Paxlovid and for 7 days after completing Paxlovid as a precaution. If you are taking hormonal contraception, as Paxlovid 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.

There is no information on the use of Paxlovid in breast-feeding. You should not breast-feed your baby while taking Paxlovid and for 7 days after completing Paxlovid 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. The recommended dose is 2 tablets of nirmatrelvir (pink tablet) with 1 tablet of ritonavir (white tablet) by mouth twice daily (in the morning and in the evening).

A course of treatment lasts 5 days. For each dose, take all 3 tablets together at the same time.

If you have kidney disease, please talk to your healthcare provider for an appropriate dose of Paxlovid.

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

If you take more Paxlovid than you should
If you take too much Paxlovid, 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 Paxlovid 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 of Paxlovid 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 Paxlovid 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
- Headache

Uncommon: may affect up to 1 in 100 people
- Allergic reactions (such as itching or skin rash)
- Abdominal pain

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)
- Feeling generally unwell

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, polyethylene glycol and iron oxide red.
- The other ingredients in the ritonavir tablet are copovidone, sorbitan laureate, colloidal anhydrous silica, anhydrous calcium hydrogen phosphate, sodium stearyl fumarate. The film-coating contains hypromellose, titanium dioxide, macrogol, hydroxypropyl cellulose, talc, colloidal anhydrous silica and polysorbate 80.

What Paxlovid looks like and contents of the pack
Paxlovid film-coated tablets are available in 5 daily-dose blister cards with a total of 30 tablets packaged in a carton.

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).

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.

Marketing Authorisation Holder

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

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

URL: https://pfi.sr/c19oralrx

Other sources of information

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

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