APPROVED
Order of the Ministry of
Health of Ukraine
08.09.2023 No. 1599
Marketing Authorisation
No. UA/20163/01/01

AMMENDED
The Order of the Ministry of
Health of Ukraine
06.09.2024 No. 1545

INSTRUCTIONS
for medical use of medicinal product

PAXLOVID

Composition:
active substance: nirmatrelvir, ritonavir;
1 pink film-coated tablet contains 150 mg of nirmatrelvir.
1 white film-coated tablet contains 100 mg of ritonavir.
excipients:
for nirmatrelvir tablet:
microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate, film coat Opadry® Pink (05B140011): HPMC 2910/hypromellose 6 cP (E464), titanium dioxide (E171), macrogol/ polyethylene glycol (E1521), iron oxide red (E172).
for ritonavir tablet: copovidone, silica, colloidal anhydrous, sorbitan laurate, calcium hydrogen phosphate, anhydrous, sodium stearyl fumarate, film coat Opadry White (20C58634)**: HPMC 2910/hypromellose 6 cP (E464), titanium dioxide (E171), macrogol/polyethylene glycol, MW 400 (E1521), hydroxypropyl cellulose (E463), talc (E553b), macrogol/polyethylene glycol, MW 3350, macrogol 4000 (E1521), silica, colloidal anhydrous (E551), polysorbate 80 (E433).

Pharmaceutical form. Film-coated tablet.
Main physical and chemical properties:
150 mg tablet: pink, oval film-coated tablet debossed with ‘PFE’ on one side and ‘3CL’ on the other side;
100 mg tablet: white to off white, capsule shaped film-coated tablet, debossed with 'H' on one side and 'R9' on other side.

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

Pharmacological properties.
Pharmacodynamics.
Mechanism of action.
Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 Main protease (M^{pro}), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of the SARS-CoV-2 M^{pro} renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication.
Ritonavir 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, and XBB.1.5 was assessed in Vero E6-TMPRSS2 cells

in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 83 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤ 1.5 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 1 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 1.

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+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 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 and treatment-emergent mutations.

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 recurrences 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 300 mg /100 mg ritonavir) 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 2 provides results of the primary endpoint in the mITT1 analysis population for the full data set at final study completion.

Table 2.
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 44/47 (6.80%) in the placebo group.

Table 3.
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) -1.45 (-2.70, -0.25)	8 (1.7%) 1.68 (0.84, 3.33)

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mITT1=modified

Table 3.
Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 analysis set

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.
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 Posology and method of administration).

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 300 mg nirmatrelvir / 100 mg ritonavir 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.

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.

Patients with renal impairment.

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

Patients with hepatic impairment.

Compared to healthy controls with no hepatic impairment, the pharmacokinetics of nirmatrelvir in 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.

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 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 OCT1 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) and dabigatran (P-gp 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.

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.

Clinical particulars.

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 *Pharmacodynamics*).

Contraindications.

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

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: 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
- 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
- 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 Interaction with other medicinal products and other forms of interaction).

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.

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 4). Coadministration of other CYP3A4 substrates that may lead to potentially significant interaction (see Table 4) 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 4 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).
↑Tamsulosin		Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6, both of which are inhibited by ritonavir. Avoid concomitant use with Paxlovid.
Amphetamine derivatives		
↑Amphetamine		Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of

	amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are coadministered with Paxlovid.
Analgesics	
↑Buprenorphine (57%, 77%)	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 dosage 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. 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).
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 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 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, ↑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.
↑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 have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (refer to the venetoclax SmPC for dosing instructions).
Anticoagulants	
↑Apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for coadministration of apixaban with Paxlovid depend on the apixaban dose. Refer to the apixaban SmPC for more information.

↑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 SmPC for further information.
↑Rivaroxaban (153%, 53%)	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of 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 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.
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.
↑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 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* ↑Fusidic acid (systemic route)	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. 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)	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when coadministered with ritonavir as a pharmacokinetic enhancer.
Rifampicin, Rifapentine	Rifampicin and rifapentine are strong CYP3A4 inducers, and this may lead to a decreased exposure of nirmatrelvir/ritonavir, 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.
Antipsychotics	
↑Clozapine	Given the risk of substantial 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, ↑Felodipine, ↑Nicardipine, ↑Nifedipine, ↑Verapamil	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when amlodipine, diltiazem, felodipine, nicardipine, nifedipine or verapamil are concomitantly administered with ritonavir.
↑Lercanidipine	Coadministration of lercanidipine and Paxlovid should be avoided.
Calcium channel antagonists	
Cardiovascular agents	
↑Aliskiren	Avoid concomitant use with Paxlovid.
↑Cilostazol	Dosage 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 dosage 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).
Dipeptidyl peptidase 4 (DPP4) inhibitors	
↑Saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin SmPC for more information.
Endothelin antagonists	
↑Bosentan	Coadministration of bosentan and ritonavir may increase steady-state bosentan maximum concentrations (C_{max}) and AUC.
↑Riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The coadministration of riociguat with Paxlovid is not recommended (refer to riociguat 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 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	
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 serum 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	Dosage 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.
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, ↑Cariprazine	Dosage adjustment of aripiprazole, brexpiprazole and cariprazine is recommended. Refer to individual SmPCs for more information.
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 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 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. 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.
↑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.

Special warnings and precautions for use.

<u>Risk of serious adverse reactions due to interactions with other medicinal products.</u>

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 Interaction with other medicinal products and other forms of interaction).

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 serum concentrations and adjusting the dose of the immunosuppressant in accordance with the latest guidelines (see section Interaction with other medicinal products and other forms of interaction).

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 4 for medicinal products that are contraindicated for concomitant use with nirmatrelvir/ritonavir and for potentially significant interactions with other medicinal products (see section Interaction with other medicinal products and other forms of interaction). Potential for interactions should be considered with other medicinal products prior to and during Paxlovid therapy; concomitant medicinal products should be reviewed during Paxlovid therapy and the patient should be monitored for the adverse reactions associated with the concomitant medicinal products.

Hypersensitivity reactions.

Anaphylaxis hypersensitivity reactions and serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported with Paxlovid (see section Undesirable effects). 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 Pharmacokinetic properties), 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.

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.

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’.

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 Interaction with other medicinal products and other forms of interaction).

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 Preclinical safety data).
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 Preclinical safety data).
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 Preclinical safety data).

Effects on ability to drive and use machines.

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

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 Special warnings and precautions for use and Pharmacokinetic properties).

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 (Child-Pugh Class C) hepatic impairment (see sections Special warnings and precautions for use and Pharmacokinetic properties).

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.

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 (see section Pharmacokinetic properties). The tablets should be swallowed whole and not chewed, broken or crushed, as no data is currently available.

Paediatric population.

The safety and efficacy of Paxlovid in patients below 18 years of age have not been established. No data are available.

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.

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 summary 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 5 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 5.

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 ADRs are also manifestations of hypersensitivity reaction.

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.

Shelf life. 2 years.

Storage conditions.
This medicinal product does not require any special storage conditions. Keep out of reach of children.

Packaging.
4 film coating tablets 150 mg and 2 film coating tablets 100 mg in blister, 5 blisters in carton box.

Dispensing conditions. By prescription.

Manufacturer.
Pfizer Manufacturing Deutschland GmbH

Manufacturer's location and address of its business activities.
Betriebsstatte Freiburg Mooswaldallee 1, 79090 Freiburg, Germany.

*or**

Manufacturer.
Pfizer Italia S.r.l.

Manufacturer's location and address of its business activities.
Localita Marino del Tronto – 63100 Ascoli Piceno (AP), Italy.

*or**

Manufacturer.
Pfizer Ireland Pharmaceuticals.

Manufacturer's location and address of its business activities.
Little Connell, Newbridge, Ireland.

** In the instructions that will be enclosed in the cardboard box, only one manufacturer (one that was involved in the batch release) will be listed.*

Date of last revision.
06.09.2024