Paxlovid™

Nirmatrelvir/Ritonavir 150 mg/100 mg

Film-coated tablets

Reference Market: UK

SUMMARY OF PRODUCT CHARACTERISTICS

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

Excipients with known effect

Each nirmatrelvir 150 mg film-coated tablet contains 176 mg of lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nirmatrelvir

Film-coated tablet (tablet).
Pink, oval, with a dimension of approximately 17.6 mm in length and 8.6 mm in width debossed with 'PFE' on one side and '3CL' on the other side.

Ritonavir

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 (see section 5.1).

4.2 Posology and method of administration

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets.

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

Posology

The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days. Paxlovid should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms.

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

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

Special populations

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

Elderly
No dose adjustment is currently recommended for elderly patients.

Renal impairment
No dose adjustment is needed in patients with mild renal impairment.
In patients with moderate renal impairment, the dose of Paxlovid should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements (see section 6.6).
Paxlovid is not recommended in patients with severe renal impairment or with renal failure as the appropriate dose has not yet been determined (see section 5.2).

Hepatic impairment
No dosage adjustment of Paxlovid is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.
No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment (Child-Pugh Class C), therefore, Paxlovid is contraindicated in patients with severe hepatic impairment.

Concomitant therapy with ritonavir- or cobicistat-containing regimen
No dose adjustment is needed; the dose of Paxlovid is 300 mg/100 mg twice daily for 5 days.
Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated.

4.3 Contraindications

Paxlovid is contraindicated in patients:
- with a history of clinically significant hypersensitivity to the active substances (nirmatrelvir/ritonavir) or to any of the excipients listed in section 6.1.
- with severe hepatic impairment.
- with severe renal impairment.

Paxlovid is also contraindicated with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. Paxlovid is also contraindicated with medicinal products that are potent CYP3A inducers where significantly reduced plasma nirmatrelvir/ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance.

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

Medicinal product class	Medicinal products within class	Clinical comments
Interactions that result in increased concentrations of concomitant medicinal product as Paxlovid inhibits their CYP3A4 metabolic pathway		
Alpha 1-adrenoreceptor antagonist	alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension.
Analgesics	pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities.
Antianginal	ranolazine	Potentially increased plasma concentrations of ranolazine may result in serious and/or life-threatening reactions.
Anticancer	neratinib venetoclax	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity. Increased plasma concentrations of venetoclax which may increase the risk risk of tumour lysis syndrome at the dose initiation and during the dose-titration phase.
Antiarrhythmics	amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Potentially increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone and quinidine may result in arrhythmias or other serious adverse effects.
Antibiotic	fusidic acid	Increased plasma concentrations of fusidic acid and ritonavir.
Anti-gout	colchicine	Increased plasma concentrations of colchicine may result in serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antihistamines	astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine may result in serious arrhythmias from these agents.
Antipsychotics/neuroleptics	lurasidone, pimozide, clozapine quetiapine	Increased plasma concentrations of lurasidone, pimozide and clozapine may result in serious and/or life-threatening reactions. Increased plasma concentrations of quetiapine may lead to coma.
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.

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

Medicinal product class	Medicinal products within class	Clinical comments
GI motility agent	cisapride	Increased plasma concentrations of cisapride, thereby increasing the risk of serious arrhythmias from this agent.
Lipid-modifying agents		
HMG-CoA reductase inhibitors	lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin resulting in increased risk of myopathy, including rhabdomyolysis.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	Increased plasma concentrations of lomitapide.
PDE5 inhibitors	avanafil, vardenafil	Increased plasma concentrations of avanafil and vardenafil.
	sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)	Increased plasma concentrations of sildenafil can potentially result in visual abnormalities, hypotension, prolonged erection and syncope.
Sedative/hypnotics	clonazepam, diazepam, estazolam, flurazepam, triazolam, oral midazolam[a]	Increased plasma concentrations of clonazepam, diazepam, estazolam, flurazepam, triazolam and oral midazolam can increase risk of extreme sedation and respiratory depression.
Interactions that result in decreased concentrations of nirmatrelvir/ritonavir as the concomitant medicinal products induce Paxlovid's CYP3A4 metabolic pathway		
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin	Decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.
Antimycobacterials	rifampin	Potentially decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.
Herbal products	St. John's Wort (*Hypericum perforatum*)	Potentially decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.

a. See section 5.2, Interaction studies conducted with nirmatrelvir/ritonavir.

4.4 Special warnings and precautions for use

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

Initiation of Paxlovid, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving Paxlovid, may increase plasma concentrations of medicinal products metabolised by CYP3A.

Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid, respectively.

These interactions may lead to:

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

See Table 1 for medicinal products that are contraindicated for concomitant use with nirmatrelvir/ritonavir (see section 4.3) and Table 2 for potentially significant interactions with other medicinal products (see section 4.5). Potential for interactions should be considered with other medicinal products prior to and during Paxlovid therapy; concomitant medicinal products should be reviewed during Paxlovid therapy and the patient should be monitored for the adverse reactions associated with the concomitant medicinal products. The risk of interactions with concomitant medications during the 5-day treatment period for Paxlovid should be weighed against the risk of not receiving Paxlovid.

Hepatotoxicity

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

HIV resistance

As nirmatrelvir is coadministered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Excipients

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Paxlovid (nirmatrelvir/ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when coadministered with nirmatrelvir/ritonavir. 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, section 4.3).

In vitro study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8, and CYP2C9. The clinical relevance is unknown. Based on *in vitro* data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Ritonavir also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of

some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products, which could decrease or shorten their therapeutic effect.

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

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

Medicinal products listed in Table 1 (section 4.3) and Table 2 are a guide and not considered a comprehensive list of all possible medicinal products that may interact with nirmatrelvir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

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

Medicinal product class	**Medicinal product within class (AUC change, C_{max} Change)**	**Clinical comments**
α1-adrenoreceptor antagonist	↑alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see section 4.3).
Amphetamine derivatives	↑methylphenidate, ↑dexamfetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are coadministered with Paxlovid.
Analgesics	↑buprenorphine (57%, 77%), ↑norbuprenorphine (33%, 108%)	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when the two are dosed together.
	↑pethidine, ↑piroxicam, ↑propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities (see section 4.3).
	↑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

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
	↓morphine	Morphine levels may be decreased due to induction of glucuronidation by coadministered ritonavir dosed as a pharmacokinetic enhancer.
Antianginal	↑ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see section 4.3).
Antiarrhythmics	↑amiodarone, ↑dronedarone, ↑flecainide, ↑propafenone, ↑quinidine	Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and is therefore contraindicated (see section 4.3).
	↑digoxin	This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer.
Antiasthmatic	↓theophylline (43%, 32%)	An increased dose of theophylline may be required when coadministered with ritonavir, due to induction of CYP1A2.
Anticancer agents	↑afatinib	Serum concentrations may be increased due to Breast Cancer Resistance Protein (BCRP) and acute P-gp inhibition by ritonavir. The extent of increase in AUC and Cmax depends on the timing of ritonavir administration. Caution should be exercised in administering afatinib with Paxlovid (refer to the afatinib SmPC). Monitor for ADRs related to afatinib.
	↑abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. 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.
	↑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

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		ritonavir resulting in the potential for serious adverse events including seizure. Concomitant use of Paxlovid with apalutamide is not recommended.
	↑ceritinib	Serum concentrations of ceritinib may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with Paxlovid. Refer to the ceritinib SmPC for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑dasatinib, ↑nilotinib, ↑vincristine, ↑vinblastine	Serum concentrations may be increased when coadministered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑encorafenib	Serum concentrations of encorafenib may be increased when coadministered with ritonavir which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Coadministration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.
	↑fostamatinib	Coadministration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Refer to the fostamatinib 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.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		Concomitant use of neratinib with Paxlovid is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (see section 4.3).
	↑venetoclax	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase (see section 4.3 and refer to the venetoclax 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, ↑dabigatran[a] (194%, 233%)	Potentially increased apixaban and dabigatran concentrations which may lead to an increased bleeding risk. Refer to apixaban and dabigatran SmPC for further information.
	↑rivaroxaban (153%, 53%)	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.
	↑vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The coadministration of vorapaxar with Paxlovid is not recommended (refer to the vorapaxar SmPC).
	warfarin, ↑↓S-warfarin (9%, 9%), ↓↔R-warfarin (33%)	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when coadministered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that anticoagulation parameters are monitored when warfarin is coadministered with ritonavir.
Anticonvulsants	carbamazepine[a]	Carbamazepine is strong CYP3A4 inducer, and this may lead to a decreased exposure of nirmatrelvir and ritonavir and potential loss of virologic response. Concomitant use of carbamazepine with Paxlovid is contraindicated (see section 4.3).

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↓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.
Antidepressants	↑amitriptyline, ↑fluoxetine, ↑imipramine, ↑nortriptyline, ↑paroxetine, ↑sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
	↑desipramine (145%, 22%)	The AUC and C_{max} of the 2-hydroxy metabolite were decreased 15% and 67%, respectively. Dosage reduction of desipramine is recommended when coadministered with ritonavir.
Anti-gout	↑colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with Paxlovid is contraindicated (see section 4.3).
Antihistamines	↑fexofenadine	Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.
	↑loratadine	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is coadministered with ritonavir.
Anti-infectives	↑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).

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑rifabutin (4-fold, 2.5-fold) ↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold)	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when 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).
	↓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.
	↑ketoconazole (3.4-fold, 55%)	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when coadministered with ritonavir.
	↑itraconazole[a], ↑erythromycin	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is coadministered with ritonavir.
	↓atovaquone	Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is 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

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline SmPC)
	delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30% increased. Due to the risk of QTc prolongation associated with DM-6705, if coadministration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid SmPC).
	↑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%, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75%.
	sulfamethoxazole/trimethoprim	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Anti-HIV protease inhibitors	↑amprenavir (64%, 5-fold)	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the SmPC for amprenavir.
	↑atazanavir (86%, 11-fold)	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. For further information, physicians should refer to the SmPC for atazanavir.
	↑darunavir (14-fold)	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. For further information, refer to the SmPC for darunavir.
	↑fosamprenavir (2.4-fold, 11-fold) measured as amprenavir)	Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. For further information, physicians should refer to the SmPC for fosamprenavir.
Anti-HIV	↑efavirenz (21%)	A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is coadministered with ritonavir.
	↑maraviroc (161%, 28%)	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the SmPC 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.
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).

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
	↑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).
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 these medicines are concomitantly administered with ritonavir.
Endothelin Antagonists	↑bosentan	Coadministration of bosentan and ritonavir may increase steady-state bosentan 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)

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
HCV Direct Acting Antiviral	↑glecaprevir/pibrentasvir	Serum concentrations may be increased due to P-gp, BCRP and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and Paxlovid is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
HMG Co-A Reductase	↑lovastatin, ↑simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir 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, ↑fluvastatin, ↑pravastatin, ↑rosuvastatin,	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	↓ethinylestradiol (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.

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
Immunosupressants	↑cyclosporine, ↑tacrolimus, ↑everolimus	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 cyclosporine, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.
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 SmPC for lomitapide) (see section 4.3).
Phosphodiesterase (PDE5) Inhibitors	↑avanafil (13-fold, 2.4-fold)	Concomitant use of avanafil with Paxlovid is contraindicated (see section 4.3).
	↑sildenafil (11-fold, 4-fold)	Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours. Concomitant use of sildenafil with Paxlovid is contraindicated in pulmonary arterial hypertension patients (see section 4.3).
	↑tadalafil (124%, ↔)	The concomitant use of tadalafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions.
	↑vardenafil (49-fold, 13-fold)	Concomitant use of vardenafil with Paxlovid is contraindicated (see section 4.3).
Sedatives/hypnotics	↑clonazepam, ↑diazepam, ↑estazolam, ↑flurazepam	Ritonavir coadministration is likely to result in increased plasma concentrations of clonazepam, diazepam, estazolam and flurazepam and is therefore contraindicated (see section 4.3).
	↑oral (1430%, 368%) and parenteral midazolam[a]	Midazolam is extensively metabolised by CYP3A4. Coadministration with Paxlovid

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, Paxlovid should not be coadministered with orally administered midazolam (see section 4.3), whereas caution should be used with coadministration of Paxlovid and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggests a possible 3 – 4 fold increase in midazolam plasma levels. If Paxlovid is coadministered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
	↑triazolam (> 20-fold, 87%)	Ritonavir coadministration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 4.3)
	↓pethidine (62%, 59%), ↑norpethidine metabolite (47%, 87%)	The use of pethidine and ritonavir is contraindicated due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (e.g., seizures) (see section 4.3).
	↑alprazolam (2.5-fold, ↔)	Alprazolam metabolism is inhibited following the introduction of ritonavir. Caution is warranted during the first several days when alprazolam is coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
	↑buspirone	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

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

Medicinal product class	Medicinal product within class (AUC change, C_{max} Change)	Clinical comments
		buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.
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	Inhaled, injectable or intranasal fluticasone propionate, budesonide, 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

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

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

Abbreviations: ATL=alanine aminotransferase, AUC= area under the curve; C_{max}= maximum concentrations.

a. See section 5.2, Interaction studies conducted with nirmatrelvir/ritonavir.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

There are no human data on the use of Paxlovid during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid.

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

Pregnancy

There are no data from the use of Paxlovid in pregnant women. Paxlovid is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

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 (see section 5.3).

A large number of pregnant women were exposed to ritonavir during pregnancy. These data largely refer to exposures where ritonavir was used in combination therapy and not at therapeutic ritonavir doses but at lower doses as a pharmacokinetic enhancer for other protease inhibitors, similar to the ritonavir dose used for nirmatrelvir/ritonavir. These data indicate no increase in the rate of birth

defects compared to rates observed in population-based birth defect surveillance systems. Animal data with ritonavir have shown reproductive toxicity (see section 5.3).

Breast-feeding

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

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

Fertility

There are no human data on the effect of Paxlovid on fertility. No human data on the effect of nirmatrelvir on fertility are available. Nirmatrelvir produced no effects on fertility in rats (see section 5.3).

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

4.7 Effects on ability to drive and use machines

There are no clinical studies that evaluated the effects of Paxlovid on ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Paxlovid is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomised, placebo-controlled trial in non-hospitalised adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection (see section 5.1). A total of 1,349 symptomatic adult participants 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either Paxlovid (nirmatrelvir/ritonavir 300 mg/100 mg) (n=672) or placebo (n=677). Study drugs were to be taken twice daily for up to 5 days.

Adverse reactions in the Paxlovid group (≥ 1%) that occurred at a greater frequency than in the placebo group were diarrhoea (3.9% and 1.9%, respectively), vomiting (1.3% and 0.3%) and dysgeusia (4.8% and 0.1%).

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (frequency cannot be estimated from the available data).

Table 3: Adverse reactions with Paxlovid

System organ class	Frequency category	Adverse reactions
Nervous system disorders	Common	Dysgeusia
Gastrointestinal disorders	Common	Diarrhoea, vomiting

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions through visiting https:// www.pfizersafetyreporting.com.

4.9 Overdose

Treatment of overdose with Paxlovid should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Paxlovid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: not yet assigned.

Mechanism of action

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

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

Antiviral activity

In vitro antiviral activity
Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{90} value of 181 nM) after Day 3 post-infection.

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

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

Pharmacodynamic effects

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

Clinical efficacy and safety

The efficacy of Paxlovid is based on the interim analysis of EPIC-HR, a Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised symptomatic adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study. Participants were randomised (1:1) to receive Paxlovid (nirmatrelvir 300 mg/ritonavir 100 mg) or placebo orally every 12 hours for 5 days. The study excluded individuals with a history of prior COVID-19 infection or vaccination. The primary efficacy endpoint is the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28 in the modified intent-to-treat (mITT) analysis set (all treated participants with onset of symptoms ≤ 3 days who had at least one post-baseline visit). Secondary efficacy endpoints included assessments of COVID-19 hospitalisation or death from any cause through Day 28 in the mITT1 analysis set (all treated participants with onset of symptoms ≤ 5 days who had at least one post-baseline visit).

A total of 1,361 participants were randomised to receive either Paxlovid or placebo. At baseline, mean age was 45 years; 52% were male; 63% were White, 5% were Black, 48% were Hispanic or Latino and 20% were Asian; 63% of participants had onset of symptoms ≤ 3 days from initiation of study treatment; 44% of participants were serological negative at baseline. The most frequently reported risk factors were BMI ≥ 25 kg/m^2 (1080 [79.4%] participants), tobacco use (501 [36.8%] participants), hypertension (441 [32.4%] participants), age ≥ 60 years (255 [18.7%] participants), and diabetes mellitus (175 [12.9%] participants). Other risk factors were cardiovascular disorder (50 [3.7%] participants), chronic kidney disease (8 [0.6%] participants), chronic lung disease (67 [4.9%] participants), immunosuppression (12 [0.9%] participants), cancer (4 [0.3%] participants), neurodevelopmental disorders (2 [0.1%] participants), HIV infection (1 [<0.1%] participant) and device dependency (5 [0.4%] participants). The mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/mL (2.78); 27% of participants had a baseline viral load of > 10^7 (units); 8.2% of participants either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses.

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

At time of the interim analysis, 389 participants in the Paxlovid group and 385 participants in the placebo group were included in the mITT analysis set. Paxlovid significantly reduced ($p<0.0001$) the proportion of participants with COVID-19 related hospitalisation or death through Day 28 by 89.1%, compared with placebo, in adult participants with symptom onset ≤ 3 days who were at increased risk of progression to severe disease. No deaths were reported in the Paxlovid group compared with 7 deaths in the placebo group. The proportions of participants who discontinued treatment due to an adverse event were 2.4% in the Paxlovid group and 4.3% in the placebo group.

Similar trends have been observed for the primary efficacy analysis across subgroups of participants. Table 4 presents the results of the primary endpoint in the mITT analysis population and in the subgroups by baseline viral load, serology status or age.

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

	Paxlovid 300 mg/100 mg	Placebo
Number of patients (%)	N=389	N=385
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	3 (0.8%) 0.78 (0.25, 2.39) -6.32 (-9.04, -3.59) p<0.0001	27 (7.0%) 7.09 (4.92, 10.17)
Viral load < 10^7 copies/mL	n=242	n=244
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	2 (0.8%) 0.83 (0.21, 3.26) -4.14 (-7.10, -1.17) p=0.0063	12 (4.9%) 4.96 (2.85, 8.57)
Viral load ≥ 10^7 copies/mL	n=122	n=117
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	1 (0.8%) 0.84 (0.12, 5.82) -10.44 (-16.44, -4.43) p=0.0007	13 (11.1%) 11.28 (6.71, 18.63)
Viral load < 10^4 copies/mL	n=124	n=119
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	0 0 -0.84 (-2.48, 0.80) p=0.3153	1 (0.8%) 0.840 (0.12, 5.82)
Viral load ≥ 10^4 copies/mL	n=240	n=242
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	3 (1.3%) 1.26 (0.41, 3.85) -8.81 (-12.89, -4.74) p<0.0001	31 (12.8%) 10.07 (6.87, 14.65)
Serology negative	n=168	n=175
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	3 (1.8%) 1.80 (0.58, 5.47) -12.17 (-17.74, -6.61) p<0.0001	24 (13.7%) 13.97 (9.59, 20.12)
Serology positive	n=217	n=204
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	0 0 0.00 (0.00, 0.00) p=0.0810	3 (1.5%) 1.48 (0.48, 4.51)
Age < 65 years	n=345	n=334
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	2 (0.6) 0.59 (0.15, 2.32) -4.88 (-7.47, -2.30) p=0.0002	18 (5.4) 5.47 (3.48, 8.54)
Age ≥ 65 years	n=44	n=51
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	1 (2.3%) 2.27 (0.32, 15.06) -15.37 (-26.73, -4.02) p=0.0079	9 (17.6%) 17.65 (9.60, 31.17)

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, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and were treated ≤ 3 days after COVID-19 symptom onset.

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

When initiated within 5 days of symptom onset, treatment with Paxlovid also significantly reduced the incidence of hospitalisation or death by 85.2% through Day 28 (Table 5). No deaths were reported in the Paxlovid group compared with 10 deaths in the placebo group. Results of the subgroup analysis for mITT1 were consistent with those for mITT.

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

	Paxlovid 300 mg/100 mg	**Placebo**
Number of patients	N=607	N=612
Patients with hospitalisation or death[a] (%) Estimated proportion over 28 days [95% CI], % Reduction relative to placebo [95% CI] p-value	6 (1.0%) 1.00 (0.45, 2.21) -5.77 (-7.92, -3.61) p<0.0001	41 (6.7%) 6.76 (5.03, 9.04)

Abbreviations: CI=confidence interval; mITT1=A modified intent-to-treat analysis set that includes 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 monoclonal antibody treatment and were treated ≤ 5 days after COVID-19 symptom onset.

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

An interim assessment of the effect of Paxlovid on viral load (copies/mL) relative to placebo was conducted. A total of 572 participants with a detectable baseline viral load were included in the interim assessment, and change from baseline to Day 5 (end of treatment) was evaluated. At Day 5, after accounting for baseline viral load level, geographic region, serology status, and symptom onset, the adjusted mean change in viral load (log_{10} copies/mL) from baseline showed an additional reduction of 0.93 log_{10} (copies/mL) in the Paxlovid group relative to placebo. The additional viral load reduction from Paxlovid treatment relative to placebo was more apparent among participants who were seronegative or had high viral load level at baseline. Similarly, among participants with symptom onset ≤ 3 days, a reduction of 1.03 log_{10} (copies/mL) was shown in the Paxlovid group relative to placebo at Day 5.

Table 6: Analysis of change from baseline to Day 5 in log_{10} (viral load, copies/mL) in adults with symptomatic COVID-19 at increased risk of progression to severe illness; mITT1 analysis set

	Paxlovid 300 mg/100 mg	**Placebo**
Number of patients	N=269	N=303
Baseline, mean (SD) Day 5, mean (SD) Adjusted change from baseline, mean (SE) Reduction relative to placebo, mean (SE)	5.41 (2.24) 2.50 (1.82) -2.69 (0.10) -0.93 (0.13)	5.11 (2.23) 3.22 (2.20) -1.75 (0.09)
Serology negative	n=128	n=135
Baseline, mean (SD) Day 5, mean (SD) Adjusted change from baseline, mean (SE) Reduction relative to placebo, mean (SE)	6.47 (1.57) 3.51 (1.54) -3.26 (0.21) -1.15 (0.20)	6.42 (1.66) 4.60 (1.91) -2.12 (0.20)
Serology positive	n=137	n=160
Baseline, mean (SD) Day 5, mean (SD) Adjusted change from baseline, mean (SE) Reduction relative to placebo, mean (SE)	4.42 (2.34) 1.54 (1.54) -2.28 (0.14) -0.77 (0.17)	4.01 (2.07) 2.15 (1.80) -1.51 (0.13)
Viral load < 10^7 copies/mL	n=183	n=228
Baseline, mean (SD) Day 5, mean (SD) Adjusted change from baseline, mean (SE)	4.26 (1.76) 1.82 (1.56) -2.04 (0.12)	4.20 (1.78) 2.51 (1.94) -1.25 (0.11)

Reduction relative to placebo, mean (SE)	-0.79 (0.15)	
Viral load ≥ 10^7 copies/mL	n=86	n=75
Baseline, mean (SD) Day 5, mean (SD) Adjusted change from baseline, mean (SE) Reduction relative to placebo, mean (SE)	7.85 (0.52) 3.98 (1.43) -4.41 (0.27) -1.40 (0.24)	7.86 (0.57) 5.30 (1.50) -3.01 (0.27)
Time from symptom onset to randomisation ≤ 3 days (mITT)	n=179	n=201
Baseline, mean (SD) Day 5, mean (SD) Adjusted change from baseline, mean (SE) Reduction relative to placebo, mean (SE)	5.73 (2.25) 2.61 (1.90) -2.99 (0.12) -1.03 (0.16)	5.46 (2.24) 3.45 (2.33) -1.96 (0.12)

Abbreviations: mITT=modified intent-to-treat. 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 monoclonal antibody treatment, and were treated ≤ 3 days after COVID-19 symptom onset; mITT1=A modified intent-to-treat analysis set that includes 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 monoclonal antibody treatment, and were treated ≤ 5 days after COVID-19 symptom onset; SD=standard deviation; SE=standard error.

Paediatric population

The Agency has deferred the obligation to submit the results of studies with Paxlovid in one or more subsets of the paediatric population in the treatment of coronavirus disease 2019 (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. In healthy participants in the fasted state, the mean half-life ($t_{1/2}$) of a single dose of 150 mg nirmatrelvir administered alone was approximately 2 hours compared to 7 hours after administration of a single dose of 250 mg/100 mg nirmatrelvir/ritonavir thereby supporting a twice-daily administration regimen.

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

Absorption

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

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV%) C_{max} and AUC_{inf} was 0.36 µg/mL (46) and 3.60 µg*hr/mL (47),

respectively. The median (range) time to C_{max} (T_{max}) was 3.98 hrs (1.48-4.20). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (2.2) hours.

Effect of food on oral absorption
Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir 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 CYP3A4. Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 in vitro at clinically relevant concentrations. In vitro study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8, and CYP2C9. The clinical relevance is unknown. Based on in vitro data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations. Administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In plasma, the only drug-related entity observed was unchanged nirmatrelvir. Minor oxidative metabolites were observed in the faeces and urine.

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

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

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

Elimination

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact drug. Approximately 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and faeces, respectively. Nirmatrelvir was the predominant drug-related entity with small amounts of metabolites arising from hydrolysis reactions in excreta. In plasma, the only drug-related entity quantifiable was unchanged nirmatrelvir.

Human studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system; approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed ritonavir.

Specific populations

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

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

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

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

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.

The effects of coadministration of Paxlovid with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarised in Table 7 (effect of other medicinal products on nirmatrelvir).

Table 7: Interactions with other medicinal products: pharmacokinetic parameters for nirmatrelvir in the presence of the coadministered medicinal products

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

Abbreviations: AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=maximum plasma concentrations.
a. For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.
b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

The effects of co-administration of Paxlovid with oral midazolam (CYP3A4 substrate) or dabigatran (P-gp substrate) on the midazolam and dabigatran AUC and C_{max}, respectively, are summarized in Table 8.

Table 8: Effect of nirmatrelvir/ritonavir on pharmacokinetics of coadministered drug

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

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

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

5.3 Preclinical safety data

Toxicology

Repeat-dose toxicity studies up to 1 month duration of nirmatrelvir in rats and monkeys resulted in no adverse findings.

Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal degeneration have been seen in all of the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of medicinal product-induced ocular changes in humans. All thyroid changes were reversible upon discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Renal changes including tubular degeneration, chronic inflammation and proteinurea were noted in rats and are felt to be attributable to species-specific spontaneous disease. Furthermore, no clinically significant renal abnormalities were noted in clinical trials.

Carcinogenesis

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

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

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

Mutagenesis

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

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

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

Reproductive toxicity

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

The potential embryo-foetal toxicity of nirmatrelvir was evaluated in the definitive rat and rabbit studies at doses up to 1,000 mg/kg/day. There was no nirmatrelvir-related effect in any of the parameters in the rat embryo-foetal development (EFD) study up to the highest dose of 1,000 mg/kg/day (exposure margin of 16x/7.8x based on total C_{max}/AUC_{24} over the predicted human exposures at a dose of 300 mg/100 mg nirmatrelvir/ritonavir twice daily). In the rabbit EFD study, there was no nirmatrelvir-related effect on foetal morphology or embryo-foetal viability up to the highest dose of 1,000 mg/kg/day (exposure margin of 24x/10x based on total C_{max}/AUC_{24}), however adverse nirmatrelvir-related lower foetal body weights (0.91x control) were observed at 1,000 mg/kg/day in the presence of nonadverse, low magnitude effects on maternal body weight change and food consumption at this dose. Growth delay is likely reversible following cessation of exposure in human, and it was not present at the intermediate dose (10x/2.8x C_{max}/AUC_{24} over the predicted clinical exposure). There were no nirmatrelvir-related severe manifestations of developmental toxicity (malformations and embryo-foetal lethality) at the highest dose tested, 1,000 mg/kg/day.

Ritonavir
Ritonavir produced no effects on fertility in rats.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nirmatrelvir

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

Film-coat:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)
Iron oxide red (E172)

Ritonavir

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25 °C.
Do not refrigerate or freeze.

6.5 Nature and contents of container

Paxlovid is packaged in cartons containing 5 daily-dose OPA/Al/PVC foil blister cards of 30 tablets. Each daily blister card contains 4 nirmatrelvir tablets and 2 ritonavir tablets.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, Kent
CT13 9NJ
United Kingdom

8. DATE OF REVISION OF THE TEXT

October 2022

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists