SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

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.

Contains sugar (lactose).

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 co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir will result in plasma concentrations of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.

Posology

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

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 hospitalisation due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course at the discretion of his/her medical practitioner.

Special populations

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 individuals 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.

Paediatric population

The safety and efficacy of PAXLOVID in patients below 18 years of age have not been established.

Method of administration

For oral use.

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 medicines that are highly dependent on Cytochrome P450 (CYP) CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. PAXLOVID is also contraindicated with medicines 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: Medicines that are contraindicated for concomitant use with PAXLOVID

Medicine class	**Medicines within class**	**Clinical comments**
Interactions that result in increased concentrations of concomitant medicine 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	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity.
	venetoclax	Increased plasma concentrations of venetoclax which may increase the risk of tumour lysis syndrome at the dose initiation and during the dose-titration phase.
Antidysrhythmics	amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Potentially increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone and quinidine may result in dysrhythmias 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 dysrhythmias from these medicines.
Antipsychotics/ neuroleptics	lurasidone, pimozide, clozapine	Increased plasma concentrations of lurasidone, pimozide and clozapine may result in serious and/or life-threatening reactions.
	quetiapine	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.
GI motility medicine	cisapride	Increased plasma concentrations of cisapride, thereby increasing the risk of serious arrhythmias from this medicine.
Lipid-modifying medicines		
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	lomitapide	Increased plasma concentrations of lomitapide.

(MTTP) inhibitor		
PDE5 inhibitors	avanafil, vardenafil sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)	Increased plasma concentrations of avanafil and vardenafil. Increased plasma concentrations of sildenafil can potentially result in visual abnormalities, hypotension, prolonged erection and syncope.
Sedative/hypnotics	clonazepam, diazepam, estazolam, flurazepam, triazolam, oral midazolam	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 medicines 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	rifampicin	Potentially decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.

Herbal medicines	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 medicines

Initiation of PAXLOVID, a CYP3A inhibitor, in patients receiving medicines metabolised by CYP3A or initiation of medicines metabolised by CYP3A in patients already receiving PAXLOVID, may increase plasma concentrations of medicines metabolised by CYP3A.

Initiation of medicines 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 medicines.
- 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 medicines that are contraindicated for concomitant use with nirmatrelvir/ritonavir (see section 4.3) and Table 2 for potentially significant interactions with other medicines (see section 4.5). Potential for interactions should be considered with other medicines prior to and during PAXLOVID therapy; concomitant medicines should be reviewed during PAXLOVID therapy and the patient should be monitored for the adverse reactions associated with the concomitant medicines. 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 co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Nirmatrelvir tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take PAXLOVID.

Nirmatrelvir and ritonavir tablets contain sodium.

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 medicines and other forms of interaction

PAXLOVID is an inhibitor of CYP3A and may increase plasma concentrations of medicines that are primarily metabolised by CYP3A. Medicines that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when co-administered with PAXLOVID. Thus, co-administration of PAXLOVID with medicines 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 medicines metabolised by these pathways and may result in decreased systemic exposure to such medicines, which could decrease or shorten their therapeutic effect.

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

PAXLOVID is a CYP3A substrate; therefore, medicines that induce CYP3A may decrease plasma concentrations of nirmatrelvir and ritonavir and reduce PAXLOVID therapeutic effect.

Medicines listed in Table 1 (section 4.3) and Table 2 are a guide and not considered a comprehensive list of all possible medicines that are contraindicated or may interact with PAXLOVID. The medical practitioner should consult appropriate references for comprehensive information.

Table 2: Interaction with other medicines and other forms of interaction

Medicine class	**Medicine 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 medicines is likely to inhibit CYP2D6 and as a result is expected to increase

		concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are co-administered with PAXLOVID.
Analgesics	↑buprenorphine (57 %, 77 %), ↑norbuprenorphine (33 %, 108 %)	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when 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 co-administered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.
	↓morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as a pharmacokinetic enhancer.
Antianginal	↑ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration with ranolazine is contraindicated (see section 4.3).
Antidysrhythmics	↑amiodarone, ↑dronedarone, ↑flecainide, ↑propafenone, ↑quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and is therefore contraindicated (see section 4.3).
	↑digoxin	This interaction may be due to modification of P-gp mediated digoxin

		efflux by ritonavir dosed as a pharmacokinetic enhancer.
Antiasthmatic	↓theophylline (43 %, 32 %)	An increased dose of theophylline may be required when co-administered with ritonavir, due to induction of CYP1A2.
Anticancer medicines	↑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 professional information (PI)). Monitor for ADRs related to afatinib.
	↑abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and PAXLOVID should be avoided. If this co-administration is judged unavoidable, refer to the abemaciclib PI 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 PAXLOVID and potential loss of virologic response. In addition, serum concentrations of apalutamide may be increased when co-administered with ritonavir resulting in the potential for serious 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 PI for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.
	↑dasatinib, ↑nilotinib, ↑vincristine, ↑vinblastine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.
	↑encorafenib	Serum concentrations of encorafenib may be increased when co-administered with ritonavir which may increase the risk of toxicity, including

		the risk of serious adverse events such as QT interval prolongation. Co-administration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, patients should be carefully monitored for safety.
	↑fostamatinib	Co-administration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Refer to the fostamatinib PI for dose reduction recommendations if such events occur.
	↑ibrutinib	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumour lysis syndrome. Co-administration of ibrutinib and ritonavir should be avoided. If the benefit is considered to outweigh the risk and ritonavir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.

	↑neratinib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with PAXLOVID is contraindicated due to serious and/or life-threatening potential reactions including hepatotoxicity (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 PI). 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 PI 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 PI for further information.

	↑rivaroxaban (153 %, 53 %)	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.
	↑vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The co-administration of vorapaxar with PAXLOVID is not recommended (refer to the vorapaxar PI).
	warfarin, ↑↓S-warfarin (9 %, 9 %), ↓↔R-warfarin (33 %)	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation; therefore it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with ritonavir.
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).
	↓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 co-administered with ritonavir. Phenytoin may decrease serum levels of ritonavir.
Antidepressants	↑amitriptyline, ↑fluoxetine, ↑imipramine, ↑nortriptyline, ↑paroxetine, ↑sertraline	Ritonavir dosed as an antiretroviral medicine 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	The AUC and C_{max} of the 2-hydroxy

	(145 %, 22 %)	metabolite were decreased 15 % and 67 %, respectively. Dosage reduction of desipramine is recommended when co-administered with ritonavir.
Anti-gout	↑colchicine	Concentrations of colchicine are expected to increase when co-administered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with PAXLOVID is contraindicated (see section 4.3).
Antihistamines	↑fexofenadine	Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.
	↑loratadine	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is co-administered with ritonavir.
Anti-infectives	↑fusidic acid	Ritonavir co-administration is likely to

		result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).
	↑rifabutin (4-fold, 2,5-fold) ↑25-*O*-desacetyl rifabutin metabolite (38-fold, 16-fold)	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when co-administered with ritonavir as a pharmacokinetic enhancer.
	rifampicin	Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of PAXLOVID and potential loss of virologic response. Concomitant use of rifampicin with PAXLOVID is contraindicated (see section 4.3).
	↓voriconazole (39 %, 24 %)	Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
	↑ketoconazole (3,4-fold, 55 %)	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose

		reduction of ketoconazole should be considered when co-administered with ritonavir.
	↑itraconazole[a], ↑erythromycin	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole and erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is co-administered with ritonavir.
	↓atovaquone	Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is co-administered with ritonavir.
	↑bedaquiline	No interaction study is available with ritonavir only. Due to the risk of bedaquiline related adverse events, co-administration should be avoided. If the benefit outweighs the risk, co-administration of bedaquiline with

		ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline PI)
	delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 was 30 % increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid PI).
	↑clarithromycin (77 %, 31 %) ↓14-OH clarithromycin metabolite (100 %, 99 %)	Due to the large therapeutic window of clarithromycin no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with ritonavir dosed as a pharmacokinetic enhancer.

		For 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.
Anti-HIV protease inhibitors	↑amprenavir (64 %, 5-fold)	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. For further information, medical practitioners should refer to the PI for amprenavir.
	↑atazanavir (86 %, 11-fold)	Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. For further information, medical practitioners should refer to the PI 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 PI 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, medical practitioners should refer to the PI 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 co-administered 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 PI for maraviroc.
	↓raltegravir (16 %, 1 %)	Co-administration 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 co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated (see section 4.3).
	↑haloperidol, ↑risperidone, ↑thioridazine	Ritonavir is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
	↑lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated (see section 4.3).
	↑quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are

		expected to increase. Concomitant administration of PAXLOVID and quetiapine is contraindicated as it may increase quetiapine-related toxicity (see section 4.3).
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 medicine 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 ↑riociguat	Co-administration of bosentan and ritonavir may increase steady-state bosentan C_{max} and AUC. Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The co-administration of riociguat with PAXLOVID is not recommended (refer

		to riociguat PI).
Ergot Derivatives	↑dihydroergotamine, ↑ergonovine, ↑ergotamine, ↑methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated (see section 4.3)
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 co-administered with ritonavir dosed as an antiretroviral medicine or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicines 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 co-administration. 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 medicine, 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 medicines or

		as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives.
Immuno-supressants	↑cyclosporine, ↑tacrolimus, ↑everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral medicine 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 medicines	↑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 PI for lomitapide) (see section 4.3).
Phosphodiesterase PDE5 Inhibitors	↑avanafil (13-fold, 2,4-fold) ↑sildenafil (11-fold, 4-	Concomitant use of avanafil with PAXLOVID is contraindicated (see section 4.3). Concomitant use of sildenafil for the

	fold)	treatment of erectile dysfunction with ritonavir dosed as an antiretroviral medicine 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 medicines 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 co-administration is likely to result in increased plasma concentrations of clonazepam, diazepam, estazolam and flurazepam and is therefore contraindicated (see section 4.3).

	↑oral (1 430 %, 368 %) and parenteral midazolam[a]	Midazolam is extensively metabolised by CYP3A4. Co-administration with PAXLOVID may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, PAXLOVID should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of PAXLOVID and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggests a possible 3 – 4 fold increase in midazolam plasma levels. If PAXLOVID is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is

		administered.
	↑triazolam (> 20-fold, 87 %)	Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated (see section 4.3)
	↓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 co-administered with ritonavir dosed as an antiretroviral medicines or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.
	↑buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral

		medicine 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.
Sleeping medicines	↑zolpidem (28 %, 22 %)	Zolpidem and ritonavir may be co-administered 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 co-

		administration.
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 medicines 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 medicine 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 medicines 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: ALT=alanine aminotransferase, AUC= area under the curve; C_{max}= maximum concentrations.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Contraception in males and females

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).

Breastfeeding

There are no data on the use of PAXLOVID in breastfeeding women.

It is unknown whether nirmatrelvir is excreted in human or animal milk, and the effects of it on the breastfed 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 breastfed newborn/infant or the effects of the medicine on milk production. A risk to the newborn/infant cannot be excluded. Breastfeeding 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 were 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 medicines 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**	**Adverse reaction**
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 medicine is important. It allows continued monitoring of the benefit / risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https:/ /www.sahpra.org.za/Publications/Index/8.

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_{50} value of 61,8 nM and EC_{90} value of 181 nM) after Day 3 post-infection. Nirmatrelvir had cell culture antiviral activity (with EC_{50} values in the low nanomolar range ≤ 3 fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621), and Omicron (B.1.1.529) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3,3 fold reduced susceptibility relative to the USA-WA1/2020 isolate.

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

No information on antiviral resistance is currently available to nirmatrelvir with SARS-CoV-2. Studies to evaluate selection of resistance to nirmatrelvir with SARS-CoV-2 in cell culture and clinical studies have not been completed. Only *in vitro* resistance selection study with murine hepatitis virus (MHV)-Mpro is available. It showed a 4,4- to 5 fold

decrease in nirmatrelvir susceptibility against mutant viruses with 5 mutations (Pro55Leu, Ser144Ala, Thr129Met, Thr50Lys, Pro15Ala) in the MHV Mpro following 10 passages in cell culture. The relevance for this to SARS-CoV-2 is not known.

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

Pharmacodynamic effects

Cardiac electrophysiology

No clinically relevant effect of nirmatrelvir on QTcF interval was observed in a double-blind, randomised, placebo-controlled, cross-over study in 10 healthy adults. The model predicted upper bound of 90 % confidence interval (CI) for baseline and ritonavir adjusted QTcF estimate was 1,96 ms at approximately 4-fold higher concentration than the mean steady-state peak concentration after a therapeutic dose of nirmatrelvir/ritonavir 300 mg/100 mg.

Effect on lipids

The changes in lipids in nirmatrelvir/ritonavir treated group were not statistically different than placebo/ritonavir treated group in an exploratory analysis of lipids in multiple ascending dose cohorts in which healthy participants were randomised to receive either escalating doses (75, 250 and 500 mg) of nirmatrelvir (n=4 per cohort) or placebo (n=2 per cohort), enhanced with ritonavir 100 mg, twice a day for 10 days.

In participants receiving placebo/ritonavir twice a day, a modest increase in cholesterol (≤ 27,2 mg/dL), LDL cholesterol (≤ 23,2 mg/dL), triglycerides (≤ 64,3 mg/dL) and decrease in HDL cholesterol (≤ 4 mg/dL) was observed. The clinical significance of such changes with short term treatment is unknown.

Clinical efficacy and safety

The efficacy of nirmatrelvir/ritonavir is based on 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. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study. Participants were randomised (1:1) to receive 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 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 monoclonal antibody (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). Secondary efficacy endpoints included assessments of COVID-19 hospitalisation or death from any cause through Day 28 in the mITT1 analysis set.

A total of 2 246 participants were randomised to receive either nirmatrelvir/ritonavir or placebo.

Table 4 provides results of the primary endpoint in the mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for nirmatrelvir/ritonavir compared to placebo was 88 % (95 % CI: 75 %, 94 %). The determination of primary efficacy was based on a planned interim analysis of 774 participants in mITT population. The estimated risk reduction was -6,3 % with a 95 % CI of (-9,0 %, -3,6 %) and 2-sided p value <0,0001.

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

	Nirmatrelvir/ ritonavir 300 mg/100 mg (N=1 039)	**Placebo** (N=1 046)
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%) Reduction relative to placebo[a] [95 % CI], %	8 (0,8) -5,62 (-7,21; -4,03)	66 (6,3)
All-cause mortality through Day 28 (%)	0	12 (1,1)

Abbreviations: CI=confidence interval.

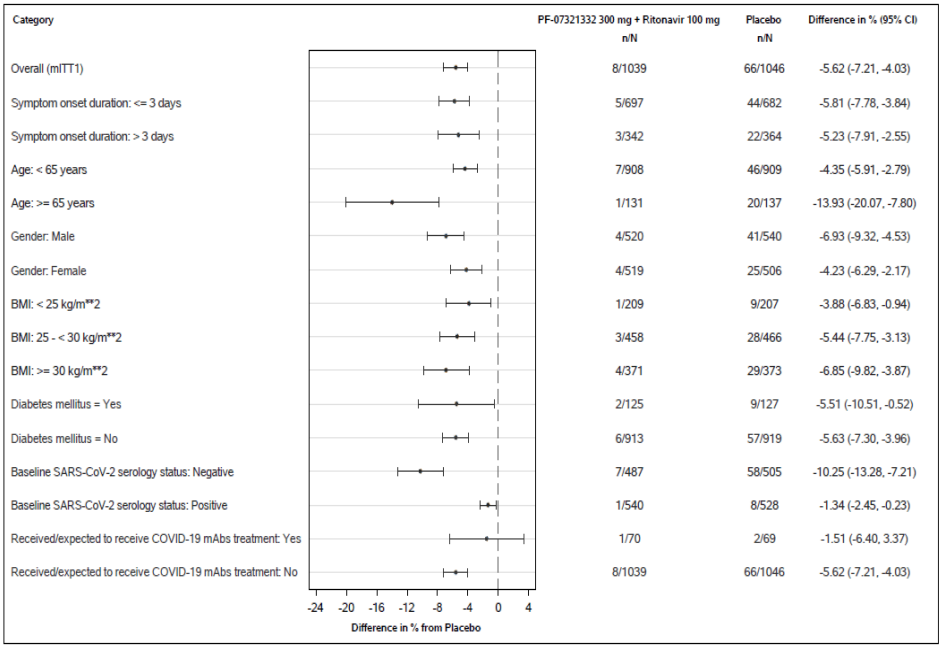
[a]. The estimated cumulative proportion of participants hospitalised or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where participants without hospitalisation and death status through Day 28 were censored at the time of study discontinuation.

No deaths were reported in the nirmatrelvir/ritonavir group compared with 12 deaths in the placebo group. The proportion of participants who discontinued treatment due to an adverse event were 2,1 % in the nirmatrelvir/ritonavir group and 4,2 % in the placebo group.

Consistent results were observed in the final mITT and mITT2 analysis populations. A total of 1 379 subjects were included in the mITT analysis population. The event rates were 5/697 (0,72 %) in the nirmatrelvir/ritonavir group, and 44/682 (6,45 %) in the placebo group. The primary SARS CoV 2 variant across both treatment arms was Delta (98,5 %), including clades 21J, 21A, and 21I.

Similar trends have been observed for the primary efficacy analysis across subgroups of participants (see Figure 1).

Figure 1: Adults with COVID-19 dosed within 5 days of symptom onset with COVID 19 related hospitalisation or death from any cause through Day 28



All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population. The difference of the proportions in the 2 treatment groups and its 95 % confidence interval based on normal approximation of the data are presented.

Relative to placebo, nirmatrelvir/ritonavir treatment was associated with an approximately 0,9 $\log_{10}$ copies/mL greater decline in viral RNA levels in nasopharyngeal samples through Day 5, with similar results observed in the mITT, mITT1, and mITT2 analysis populations.

Paediatric population

Please see section 4.2.

5.2 Pharmacokinetic properties

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

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations of nirmatrelvir. In healthy participants in the fasted state, the mean half-life ($t_{1/2}$) of a single dose of 150 mg nirmatrelvir

administered alone was approximately 2 hours compared to 7 hours after administration of a single dose of 250 mg/100 mg nirmatrelvir/ritonavir thereby supporting a twice-daily administration regimen.

Upon administration of single dose of nirmatrelvir/ritonavir 250 mg/100 mg to healthy participants in the fasted state, the geometric mean (CV %) maximum concentration (C_{max}) and area under the plasma concentration-time curve from 0 to the time of last measurement (AUC_{last}) was 2,88 ug/mL (25 %) and 27,6 ug*hr/mL (13 %), respectively. Upon repeat-dose of nirmatrelvir/ritonavir 75 mg/100 mg, 250 mg/100 mg, and 500 mg/100 mg administered twice daily, the increase in systemic exposure at steady-state appears to be less than dose proportional. Multiple dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 were similar to Day 10 across all doses.

Absorption

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean nirmatrelvir (CV %) C_{max} and area under the plasma concentration-time curve from 0 to infinity (AUC_{inf}) at steady-state was 2,21 µg/mL (33) and 23,01 µg*hr/mL (23), respectively. The median (range) time to C_{max} (T_{max}) was 3,00 hrs (1,02 - 6,00). The arithmetic mean (+SD) terminal elimination half-life was 6,1 (1,8) hours.

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV %) C_{max} and AUC_{inf} was 0,36 µg/mL (46) and 3,60 µg*hr/mL (47), respectively. The median (range) time to C_{max} (T_{max}) was 3,98 hrs (1,48 – 4,20). The arithmetic mean (+SD) terminal elimination half-life was 6,1 (2.2) hours.

Effect of food on oral absorption

Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15 % increase in mean C_{max} and 1,6 % increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir co-administered with ritonavir tablets.

Distribution

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

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

Biotransformation

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

In vitro studies utilising human liver microsomes have demonstrated that 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 medicines 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 medicines metabolised by these pathways and may result in decreased systemic exposure to such medicines, 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 medicine. 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 medicine-related entity with small amounts of metabolites

arising from hydrolysis reactions in excreta. In plasma, the only medicine-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.

Special populations

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

Racial or ethnic groups

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

Patients with renal impairment

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

Patients with hepatic impairment

Compared to healthy controls with no hepatic impairment, the PK of nirmatrelvir in individuals 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 medicines that are primarily metabolised by CYP3A. Despite being co-administered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of nirmatrelvir.

The effects of co-administration of nirmatrelvir/ritonavir with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarised in Table 5 (effect of other medicines on nirmatrelvir).

Table 5: Interactions with other medicines: pharmacokinetic parameters for nirmatrelvir in the presence of the co-administered medicine

Co-administered medicine	**Dose (schedule)**		**N**	**Ratio (in combination with co-administered medicine/alone) of nirmatrelvir pharmacokinetic parameters (90 % CI); no effect=100**	
	Co-administered medicine	**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 nirmatrelvir/ritonavir with oral midazolam (CYP3A4 substrate) or dabigatran (P-gp substrate) on the midazolam and dabigatran AUC and C_{max}, respectively, are summarized in Table 6.

Table 6: Effect of nirmatrelvir/ritonavir on pharmacokinetics of co-administered medicine

Co-administered medicine	**Dose (schedule)**		**N**	**Percent ratio[a] of test/reference of geometric means (90 % CI); no effect=100**	
	Co-administered medicine	**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 medicine-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

Nirmatrelvir/ritonavir 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

Nirmatrelvir/ritonavir 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.

Embryo-foetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1 000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and 7 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1 000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 8x higher than clinical exposures at the authorised human dose of nirmatrelvir/ritonavir. In the rabbit EFD study, lower foetal body weights (9 % decrease) were observed at 1 000 mg/kg/day in the absence of significant maternal toxicity findings. At 1 000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 10x higher than clinical

exposures at the authorised human dose of nirmatrelvir/ritonavir. No other significant developmental toxicities (malformations and embryo-foetal lethality) were observed at up to the highest dose tested, 1 000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3x higher than clinical exposures at the authorised human dose of nirmatrelvir/ritonavir.

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 at systemic exposures (AUC) approximately 4 times higher than exposure at the authorised human dose of nirmatrelvir/ritonavir. 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, at systemic exposures approximately 4 times higher than exposure at the authorised human dose of nirmatrelvir/ritonavir. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the authorised human dose of nirmatrelvir/ritonavir. In the rabbit, resorptions, decreased litter size and decreased foetal weights were observed at maternally toxic doses approximately 11 times higher than the authorised human dose of nirmatrelvir/ritonavir, based on a body surface area conversion factor. 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, at ritonavir doses 3 times higher than the authorised human dose of nirmatrelvir/ritonavir, based on a body surface area conversion factor.

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 film-coated tablets

Tablet core

Copovidone

Sorbitan laureate

Silica, colloidal anhydrous (E551)

Calcium hydrogen phosphate, anhydrous

Sodium stearyl fumarate

Film coat

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol (E1521)

Hydroxypropyl cellulose (E463)

Talc (E553b)

Silica, colloidal anhydrous (E551)

Polysorbate 80 (E433)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or 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 medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

57/20.2.8/0360

9. DATE OF FIRST AUTHORISATION

24 January 2023

10. DATE OF REVISION OF THE TEXT

N/A