▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – PAXLOVID® (nirmatrelvir/ritonavir tablets)

1. NAME OF THE MEDICINE

PAXLOVID contains nirmatrelvir tablets co-packaged with ritonavir tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nirmatrelvir film-coated tablet contains 150 mg of nirmatrelvir.

Each ritonavir film-coated tablet contains 100 mg ritonavir.

Excipient(s) with known effect

Each nirmatrelvir tablet contains 176 mg lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Nirmatrelvir

Nirmatrelvir tablets are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.

Ritonavir

Ritonavir tablets are white to off-white film coated oval tablets debossed with “NK” on one side; or white to off white, capsule shaped, film-coated tablets, debossed with 'H' on one side and 'R9' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PAXLOVID is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults 18 years of age and older, who do not require initiation of supplemental oxygen due to COVID-19 and are at increased risk of progression to hospitalisation or death (see Section 5.1 Pharmacodynamic properties, Clinical trials).

4.2 Dose and method of administration

Nirmatrelvir must be taken together with ritonavir. Failure to correctly take nirmatrelvir with ritonavir will result in plasma levels of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.

Dosage

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

PAXLOVID should be taken as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptoms onset even if baseline COVID-19 symptoms are mild. PAXLOVID treatment should not be initiated in patients requiring hospitalisation due to severe or critical COVID-19. 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 their healthcare provider.

PAXLOVID (both nirmatrelvir and ritonavir tablets) can be taken with or without food (see Section 5.2 Pharmacokinetic properties). The tablets should be swallowed whole and not chewed, broken, or crushed.

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

Dose adjustment

Mild renal impairment

No dose adjustment is needed in patients with mild renal impairment [estimated glomerular filtration rate (eGFR) ≥60 to <90 mL/min/1.73m^2].

Moderate or severe renal impairment

In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73m^2) or with severe renal impairment (eGFR <30 mL/min/1.73m^2) including those requiring haemodialysis, the dosage of PAXLOVID should be reduced as shown in Table 1.

PAXLOVID should be administered at approximately the same time each day for 5 days. On days patients with severe renal impairment undergo haemodialysis, the PAXLOVID dose should be administered after haemodialysis (see Section 5.2 Pharmacokinetic properties).

Table 1: **Recommended dose and regimen for patients with renal impairment**

Renal function	Days of treatment	Dose and dose frequency[a]
Moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73m^2)	Days 1-5	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) **twice daily**
Severe renal impairment (eGFR <30 mL/min/1.73m^2)	Day 1	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) **once**

including those requiring haemodialysis[b]	Days 2-5	150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) **once daily**

Abbreviation: eGFR=estimated glomerular filtration rate.

a. PAXLOVID should be administered at approximately the same time each day for 5 days.

b. On days of haemodialysis, the PAXLOVID dose should be administered after haemodialysis.

Special attention for patients with severe renal impairment

Healthcare professionals should pay special attention to dosing instructions for patients with severe renal impairment and alert the patient that the daily dose pack provided may contain more nirmatrelvir and ritonavir tablets than needed for accurate dosing in these patients.

Therefore, patients with severe renal impairment should be alerted that two tablets of nirmatrelvir with one tablet of ritonavir should be taken once on day 1 followed by one tablet of nirmatrelvir with one tablet of ritonavir once daily on days 2 to 5.

Special attention for patients with moderate renal impairment

Healthcare professionals should pay special attention to dosing instructions for patients with moderate renal impairment and alert the patient that the daily dose pack provided may contain more nirmatrelvir and ritonavir tablets than needed for accurate dosing in these patients.

Therefore, patients with moderate renal impairment should be alerted that only one tablet of nirmatrelvir with one tablet of ritonavir should be taken every 12 hours for 5 days.

Hepatic impairment

Mild and Moderate

No dosage adjustment of PAXLOVID is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Severe

No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with (Child-Pugh Class C) severe hepatic impairment, therefore, PAXLOVID is contraindicated in patients with severe hepatic impairment (see Sections 4.3 Contraindications and 5.2 Pharmacokinetic properties).

Paediatric use

The safety and efficacy of PAXLOVID in paediatric patients younger than 18 years of age have not yet been established. No data are available.

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 reactions to its active ingredients (nirmatrelvir/ritonavir) or any other components of the product listed in Section 6.1 List of excipients.

PAXLOVID is contraindicated in patients with severe hepatic impairment.

PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions (see Section 4.5 Interactions with other medicines and other forms of interactions). Drugs listed in this section and section 4.5 are a guide and not considered a comprehensive list of all possible drugs that may be contraindicated with PAXLOVID.

Table 2: Medicinal products that are contraindicated for concomitant use with PAXLOVID and are associated with serious and/or life-threatening reactions

Medicinal product class	**Medicinal products within class**
Interactions that result in an increase or decrease in concentrations of concomitant medicine	
Alpha 1-adrenoreceptor antagonist	alfuzosin
Antianginal	ranolazine
Antiarrhythmics	amiodarone, flecainide
Anticancer	neratinib, venetoclax
Anti-gout	colchicine
Antipsychotics	lurasidone, clozapine, cariprazine
Benign prostatic hyperplasia agents	silodosin
Cardiovascular agents	eplerenone, ivabradine
Ergot derivatives	ergometrine
Lipid-modifying agents HMG-CoA reductase inhibitors	simvastatin
Opioid analgesic	pethidine
Migraine medications	eletriptan
Mineralocorticoid receptor antagonists	finerenone
Opioid antagonists	naloxegol
PDE5 inhibitor when used for pulmonary arterial hypertension (PAH)	sildenafil
PDE5 inhibitor when used for erectile dysfunction	avanafil, vardenafil
Sedative/hypnotics	diazepam, triazolam, oral midazolam, zolpidem
Vasopressin receptor antagonists	tolvaptan

PAXLOVID is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after

discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer (see Section 4.5 Interactions with other medicines and other forms of interactions):

Table 3: Medicinal products that are contraindicated for concomitant use with PAXLOVID and associated potential loss of virologic response and possible resistance.

Interactions that result in decrease in nirmatrelvir/ritonavir concentrations	
Anticancer	apalutamide, enzalutamide
Anticonvulsant	carbamazepine[a], phenobarbital, phenytoin, primidone
Antimycobacterials	rifampicin
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor
Herbal products	St. John's Wort (*hypericum perforatum*)

a. See Section 5.2 Pharmacokinetics properties, Drug 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 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 medications.
- Clinically significant adverse reactions from greater exposures of PAXLOVID.
- Loss of therapeutic effect of PAXLOVID and possible development of viral resistance.

Severe, life-threatening, and fatal adverse reactions due to drug interactions have been reported in patients treated with PAXLOVID.

See Table 2 for medicinal products that are contraindicated for concomitant use with PAXLOVID (see Section 4.3 Contraindications) and Table 3 for potentially significant interactions with other medicinal products (see Section 4.5 Interaction with other medicines and other forms of interaction). Consider the potential for interactions with other medicinal products prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications.

Co-administration of PAXLOVID with calcineurin inhibitors and mTOR inhibitors

Consultation of a multidisciplinary group (e.g., involving physicians, specialists in immunosuppressive therapy, and/or specialists in clinical pharmacology) is required to handle the complexity of this co-administration by closely and regularly monitoring immunosuppressant blood concentrations and adjusting the dose of the immunosuppressant in accordance with the latest guidelines (see Section 4.5 Interactions with other medicines and other forms of interactions).

Hypersensitivity reactions

Anaphylaxis, hypersensitivity reactions, and serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported with PAXLOVID (see Section 4.8 Adverse effects (undesirable effects)). If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care.

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 (See Section 4.2 Dose and method of administration, Hepatic impairment).

Risk of HIV-1 resistance development

As 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.

Excipients

PAXLOVID contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. The level of lactose within this preparation should not routinely preclude the use of this medication in those with galactosaemia.

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

Use in 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 not recommended for use in patients with severe hepatic impairment (see Sections 4.2 Dose and method of administration, Hepatic impairment, 4.3 Contraindications and 5.2 Pharmacokinetic properties, Hepatic impairment)

Use in renal impairment

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment (see Section 5.2 Pharmacokinetic properties).

No dose adjustment is needed in patients with mild renal impairment. In patients with moderate to severe renal impairment the dose of PAXLOVID should be reduced. (See Section 4.2 Dose and method of administration, Renal impairment).

Use in the elderly

Clinical studies of PAXLOVID include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy (see Section 4.8 Adverse effects (undesirable effects), Section 5.1 Pharmacodynamic properties, Clinical trials). Of the total number of participants in EPIC-HR randomised to receive PAXLOVID (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

Paediatric use

The safety and efficacy of PAXLOVID in paediatric patients younger than 18 years of age have not yet been established. No data available.

Effects on laboratory tests

Ritonavir has been associated with alterations in cholesterol, triglycerides, AST, ALT, GGT, CPK and uric acid (see also Section 4.4 Special warnings and precautions for use, Use in Hepatic impairment). For comprehensive information concerning laboratory test alterations associated with nucleoside analogues, physicians should refer to the complete product information for each of these drugs.

4.5 Interactions with other medicines and other forms of interactions

PAXLOVID (nirmatrelvir/ritonavir) is a strong inhibitor of CYP3A and an inhibitor of CYP2D6, P-gp and OATP1B1. Co-administration of PAXLOVID with drugs that are primarily metabolised by CYP3A and CYP2D6 or are transported by P-gp or OATP1B1 may result in increased plasma concentrations of such drugs and increase the risk of adverse reactions.

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 co-administered with nirmatrelvir/ritonavir. Thus, co-administration of PAXLOVID 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 2, Section 4.3 Contraindications).

Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8 and CYP1A2 or UGT1A1, UGT1A4, UGTA6, UGT1A9, UGT2B7 and UGTB15 *in vitro* at clinically relevant concentrations. Nirmatrelvir is unlikely to be an inducer of CYP1A2, CYP2C19, CYP2B6, CYP2C8 and CYP2C9 enzymes. Based on *in vitro* data, nirmatrelvir has a low potential to inhibit BCRP, MATE1, MATE2K, OAT1, OAT3, OATP1B3, OCT1 and OCT2.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6 > CYP2C9, CYP2C19 >> CYP2A6, CYP1A2, CYP2E1. 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 decease or shorten their therapeutic effect.

Co-administration of other CYP3A4 substrates that may lead to potentially significant drug interactions should be considered only if the benefits outweigh the risks (see Table 3).

Nirmatrelvir and ritonavir are CYP3A substrates; therefore, medicinal products that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce PAXLOVID therapeutic effect.

The drug-drug interactions listed in Table 2 (see Section 4.3 Contraindications) and Table 3 correspond to drug-drug interactions related to ritonavir. As a conservative approach, they should also apply for PAXLOVID.

Medicinal products listed in Table 2 (Section 4.3 Contraindications) and Table 3 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 4: Established and potentially significant interactions with other medicines

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension (see Section 4.3 Contraindications).
	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Analgesics	pethidine	↑ pethidine	Co-administration with pethidine is contraindicated due to potential for serious respiratory depression (see Section 4.3 Contraindications).
	piroxicam	↓ piroxicam	Decreased piroxicam exposure due to CYP2C9 induction by PAXLOVID.
	fentanyl, hydrocodone, oxycodone	↑ fentanyl ↑ hydrocodone ↑ oxycodone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone or oxycodone is concomitantly administered with PAXLOVID. If concomitant use with PAXLOVID is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual Product Information for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions (see Section 4.3 Contraindications).
Antiarrhythmics	amiodarone, flecainide	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias (see Section 4.3 Contraindications).
Antiarrhythmics	lidocaine (systemic), disopyramide	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide, enzalutamide	↓ nirmatrelvir/ ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance (see Section 4.3 Contraindications).
	afatinib	↑ afatinib	Caution should be exercised when afatinib is coadministered with PAXLOVID (refer to the afatinib Product Information).
	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant haematologic or gastrointestinal side effects. For further information, refer to individual Product Information for anticancer drugs.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticoagulants	warfarin	↑↓ warfarin	Closely monitor INR if co-administration with warfarin is necessary.
	rivaroxaban	↑ rivaroxaban	Increased bleeding risk with rivaroxaban. Avoid concomitant use.
	dabigatran[a]	↑ dabigatran	Increased bleeding risk with dabigatran. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran Product Information for further information.
	apixaban	↑ apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with PAXLOVID depend on the apixaban dose. Refer to the apixaban Product Information for more information.
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin, primidone	↓ nirmatrelvir/ ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and possible resistance (see Section 4.3 Contraindications).
	clonazepam	↑ clonazepam	Co-administration with ritonavir will likely increase plasma concentrations of clonazepam and can increase risk of extreme sedation and respiratory depression.
	lamotrigine	↓ lamotrigine	Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are co-administered with ritonavir.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antidepressants	amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	↑ amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
Antifungals	voriconazole, ketoconazole, isavuconazonium sulfate, itraconazole[a]	↓ voriconazole ↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ ritonavir	Avoid concomitant use of voriconazole. Refer to the ketoconazole, isavuconazonium sulfate, and itraconazole Product Information for further information.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see Section 4.3 Contraindications).
Anti-HIV protease inhibitors	atazanavir, darunavir, fosamprenavir, saquinavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' Product Information. Patients on ritonavir-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use of these protease inhibitors (see Section 4.2 Dose and method of administration).

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-HIV	efavirenz, maraviroc, nevirapine, raltegravir, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↔ nevirapine ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs' Product Information.
Antihistamine	loratadine	↑ loratadine	Careful monitoring of therapeutic and adverse effects is recommended when loratadine is co-administered with ritonavir.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective Product Information for anti-infective dose adjustment.
	atovaquone	↓ atovaquone	Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is co-administered with ritonavir.
Antimycobacterial	rifampicin	↓ nirmatrelvir/ ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered (see Section 4.3 Contraindications).
	rifabutin	↑ rifabutin	Refer to the rifabutin Product Information for further information on rifabutin dose reduction.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antiparasitic agent	albendazole	↓ albendazole	Significant decreases in plasma concentrations of albendazole and its active metabolite may occur due to induction by ritonavir, with a risk of decreased albendazole efficacy. Clinical monitoring of therapeutic response and possible adjustment of albendazole dosage during treatment with PAXLOVID and following discontinuation is recommended.
Antipsychotics	lurasidone, clozapine	↑ lurasidone ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias (see Section 4.3 Contraindications).
	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine Product Information for recommendations.
Antipsychotics	haloperidol, risperidone	↑ haloperidol ↑ risperidone	Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension (see Section 4.3 Contraindications).

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Calcium channel blockers	amlodipine, diltiazem, felodipine, nifedipine, verapamil	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. If co-administered, refer to the individual Product Information for calcium channel blocker for further information.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised when co-administering PAXLOVID with digoxin, with appropriate monitoring of serum digoxin levels. Refer to the digoxin Product Information for further information.
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalaemia (see Section 4.3 Contraindications).
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances (see Section 4.3 Contraindications).
	ticagrelor clopidogrel	↑ ticagrelor ↓ clopidogrel active metabolite	Avoid concomitant use with PAXLOVID.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	mavacamten	↑ mavacamten	Co-administration with mavacamten may increase mavacamten plasma concentration and increase the risk of heart failure. Discontinue mavacamten for the duration of PAXLOVID treatment. Resumption of mavacamten within 5 days of completing PAXLOVID may result in higher exposure of mavacamten. Refer to the mavacamten Product Information for more information.
Corticosteroids primarily metabolised by CYP3A	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, triamcinolone	↑ corticosteroid	Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. However, the risk of Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. Alternative corticosteroids including beclomethasone and prednisolone should be considered.
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ nirmatrelvir/ ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance (see Section 4.3 Contraindications).

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	ivacaftor elexacaftor/ tezacaftor/ivacaftor tezacaftor/ivacaftor	↑ ivacaftor ↑ elexacaftor/ tezacaftor/ivacaftor ↑ tezacaftor/ ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to the individual Product Information for more information.
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin Product Information for more information.
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan Product Information for further information.
Ergot derivatives	ergometrine	↑ ergometrine	Co-administration of ergometrine with PAXLOVID is contraindicated (see Section 4.3 Contraindications).
Hepatitis C direct acting antivirals	glecaprevir/ pibrentasvir sofosbuvir/ velpatasvir/ voxilaprevir	↑ antiviral	Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID. Refer to the sofosbuvir/velpatasvir/voxilaprevir Product Information for further information. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use (see Section 4.2 Dose and method of administration).

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Herbal products	St. John's Wort (hypericum perforatum)	↓ nirmatrelvir/ ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance (see Section 4.3 Contraindications).
HMG-CoA reductase inhibitors	simvastatin	↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis (see Section 4.3 Contraindications). Discontinue use of simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
	atorvastatin, rosuvastatin[a]	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID.
Hormonal contraceptive	ethinylestradiol	↓ ethinylestradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	Calcineurin inhibitors: ciclosporin, tacrolimus mTOR inhibitors: sirolimus, everolimus	↑ ciclosporin ↑ tacrolimus ↑ sirolimus ↑everolimus	Avoid concomitant use of calcineurin inhibitors and mTOR inhibitors during treatment with PAXLOVID. Dose adjustment of the immunosuppressant and close and regular monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions are recommended during and after treatment with PAXLOVID. Refer to the individual immunosuppressant Product Information and latest guidelines for further information and obtain expert consultation of a multidisciplinary group (see Section 4.4 Special warnings and precautions for use).
Janus kinase (JAK) inhibitors	tofacitinib	↑ tofacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib Product Information for more information.
	upadacitinib	↑ upadacitinib	Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib Product Information for more information.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Avoid concomitant use with PAXLOVID. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
Migraine medications	eletriptan	↑ eletriptan	Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events (see Section 4.3 Contraindications).
	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalaemia, hypotension, and hyponatremia (see Section 4.3 Contraindications).
Muscarinic receptor antagonists	darifenacin	↑ darifenacin	The darifenacin daily dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin Product Information for more information.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with PAXLOVID.
	aripiprazole, brexpiprazole	↑ aripiprazole ↑ brexpiprazole	Dosage adjustment of aripiprazole, brexpiprazole is recommended. Refer to the individual Product Information for more information.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	cariprazine	↑ cariprazine	Coadministration is contraindicated due to increased plasma exposure of cariprazine and its active metabolites (see Section 4.3 Contraindications).
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities hypotension, prolonged erection, and syncope (see Section 4.3 Contraindications).
	tadalafil	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Co-administration of riociguat with PAXLOVID is not recommended (refer to riociguat Product Information).
Erectile dysfunction agents (PDE5 inhibitors)	vardenafil	↑ vardenafil	Concomitant use of vardenafil with PAXLOVID is contraindicated (see section 4.3 Contraindications).
	avanafil	↑ avanafil	Co-administration contraindicated because a safe and effective avanafil dosage regimen has not been established (see Section 4.3 Contraindications).
	sildenafil, tadalafil	↑ sildenafil ↑ tadalafil	Dosage adjustment is recommended for use of sildenafil or tadalafil with PAXLOVID. Refer to the individual Product Information for more information.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms (see Section 4.3 Contraindications).
Sedative/hypnotics	buspirone clorazepate	↑ sedative/hypnotic	A dose decrease may be needed when co-administered with PAXLOVID and monitoring for adverse events.
	midazolam (administered parenterally)	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam Product Information for further information.
	diazepam, zolpidem	↑ diazepam ↑ zolpidem	Co-administration of diazepam and zolpidem with ritonavir is contraindicated (see section 4.3 Contraindications).
	alprazolam	↑ alprazolam	Caution is warranted during the first several days when alprazolam is co-administered with ritonavir before induction of alprazolam metabolism develops.
	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression (see section 4.3 Contraindications).

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Smoking cessation	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalaemia (see Section 4.3 Contraindications).

a. See Section 5.2 Pharmacokinetic properties, Drug interaction studies conducted with nirmatrelvir/ritonavir.

4.6 Fertility, pregnancy and lactation

Effects on fertility

There are no human data on the effect of PAXLOVID on fertility.

Nirmatrelvir

No human data on the effect of nirmatrelvir on fertility are available.

There were no nirmatrelvir-related effects on fertility and reproductive performance in male and female rats treated orally at doses up to 1,000 mg/kg/day for 14 days before mating, resulting in systemic exposure approximately 5 times the human exposure based on total AUC at the recommended clinical dose.

Ritonavir

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

Use in pregnancy – Category B3

PAXLOVID is not recommended during pregnancy and in women of childbearing potential not using contraception.

There are limited human data on the use of PAXLOVID during pregnancy to evaluate the drug-associated risk of adverse developmental outcomes; women of childbearing potential should avoid becoming pregnant during treatment and until after 7 days after stopping PAXLOVID.

Nirmatrelvir

The potential embryo-fetal toxicity of nirmatrelvir was evaluated in rats and rabbits. Animal data with nirmatrelvir have shown developmental toxicity in rabbits (lower fetal body weights) but not in rats. There was no nirmatrelvir-related effect on rat embryo-fetal development up to the highest dose of 1,000 mg/kg/day (10 times the human exposure based on total AUC at the recommended clinical dose). In the rabbit embryo-fetal development study, adverse nirmatrelvir-related lower fetal body weights (9% decrease) were observed at the highest dose of 1,000 mg/kg/day (13 times the human exposure based on total AUC at the recommended clinical dose) in the presence of low magnitude effects on maternal body weight change and food consumption. These findings were not present at the intermediate dose of 300 mg/kg/day (14x/3.6x C_{max}/AUC_{24} over the predicted clinical exposure).

There were no nirmatrelvir-related adverse effects in a pre- and postnatal developmental study in rats. In a pre- and postnatal developmental study in rats dosed with nirmatrelvir from gestation day 6 to lactation day 20, lower body weights (up to <8% lower than that of the control group on postnatal day 17) were observed in the offspring of pregnant rats at 1000 mg/kg/day (10 times the human exposure based on total AUC at the recommended clinical dose). No significant differences in offspring body weight were observed from PND 28 to PND 56. No body weight changes in the offspring were noted at 300 mg/kg/day (6 times the human exposure based on total AUC at the recommended clinical human dose).

Ritonavir

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with PAXLOVID, and during a menstrual cycle after stopping PAXLOVID (see Section 4.5 Interactions with other medicines and other forms of interactions).

A large number of pregnant women exposed to ritonavir during pregnancy indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems. Based on the review of data from the US Antiretroviral (ART) Pregnancy Registry through 31 July 2016, among women exposed to ritonavir-containing antiretroviral therapy (ART) during first trimester the prevalence rate of birth defects per 100 live births (65 cases in 2,983 enrolled) was 2.2% (95% CI 1.7, 2.8%). The prevalence rate of birth defects for exposure to ritonavir-containing ART during second/third trimester (97 cases in 3,330 enrolled) was 2.9% (95% CI 2.4%, 3.5%). In a reference population in the US CDC's birth defects surveillance system (MACDP) the reported background rate of birth defects is 2.7%. 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 PK enhancer for other protease inhibitors, similar to the ritonavir dose used for nirmatrelvir/ritonavir.

No treatment-related malformations were observed when ritonavir was administered orally to pregnant rats or rabbits. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dosage of 75 mg/kg/day. A slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day. Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased fetal weights) also occurred at a maternally toxic dosage of 110 mg/kg/day. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in lactation

In a clinical pharmacokinetics study, 8 healthy lactating women who were at least 12 weeks postpartum were administered 3 doses (steady-state dosing) of 300 mg/100 mg nirmatrelvir/ritonavir. Nirmatrelvir and ritonavir were excreted in breastmilk in small amounts, with a milk to plasma AUC ratio of 0.26 and 0.07, respectively. The estimated daily infant dose (assuming average milk consumption of 150 mL/kg/day), was 1.8% and 0.2% of the maternal dose.

There are no available data on the effects of nirmatrelvir or ritonavir on the breastfed newborn/infant or on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with PAXLOVID and for 48 hours after completing PAXLOVID treatment.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

The safety of PAXLOVID is based on data from three phase 2/3 randomised, placebo-controlled trials in adult participants 18 years of age and older (see Section 5.1 Pharmacodynamic properties):

- Study C4671005 (EPIC-HR) and Study C4671002 (EPIC-SR) investigated PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) every 12 hours for 5 days in symptomatic participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Participants had mild to moderate COVID-19 disease at baseline.
- Study C4671006 (EPIC-PEP) investigated PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) every 12 hours for 5 or 10 days in asymptomatic household contact of individuals with a recent diagnosis of SARS-CoV-2 infection. Participants were to have a negative SARS-CoV-2 result at baseline.

Across the three studies, 3,515 participants received a dose of PAXLOVID and 2,585 participants received a dose of placebo. The most common adverse reactions (≥1% incidence in the PAXLOVID group and occurring at a greater frequency than in the placebo group) were dysgeusia (5.9% and 0.4%, respectively) and diarrhoea (2.9% and 1.9%, respectively).

Based on limited data from a Phase 1, open-label study, the safety profile of PAXLOVID in 15 participants with severe renal impairment, including those requiring haemodialysis, was consistent with the safety profile observed in the placebo-controlled trials.

In Study C4671005 (EPIC-HR), the proportions of subjects who discontinued treatment due to an adverse event were 21 (2.0%) in the PAXLOVID group and 45 (4.3%) in the placebo group. The proportion of subjects with serious adverse events were 18 (1.7%) and 71 (6.7%) in the PAXLOVID group and in the placebo group, respectively.

Table 5: Adverse Drug Reaction Table with Preferred Terms Listed by Decreasing Frequency Within Each System Organ Class

System Organ Class	ADR Term	Frequency n/N (%)
Immune system disorders	Hypersensitivity*	21/3515 (0.60%)
	Anaphylaxis*	3/3515 (0.09%)
Nervous system disorders	Dysgeusia[a]	208/3515 (5.92%)
	Headache[a]	50/3515 (1.42%)
Vascular disorders	Hypertension*	18/3515 (0.51%)
Gastrointestinal disorders	Diarrhoea[a]	102/3515 (2.90%)
	Nausea*	63/3515 (1.79%)
	Vomiting[a]	33/3515 (0.94%)
	Abdominal pain*	11/3515 (0.31%)
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis*	3/3515 (0.09%)
	Stevens-Johnson syndrome*	3/3515 (0.09%)
General disorders and administration site conditions	Malaise*	1/3515 (0.03%)

* Adverse drug reaction (ADR) identified post-marketing.

a. Occurring at a ≥1% frequency in the PAXLOVID group and at a greater frequency than in the placebo group and/or likely associated with PAXLOVID based on available data and causality assessment.

The adverse drug reactions in the Table below 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 6: Adverse Drug Reactions by System Organ Class and Council for International Organisations of Medical Sciences (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and System Organ Class

System Organ Class	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	Very Rare < 1/10,000	Frequency not known[b]
Immune system disorders			Hypersensitivity*	Anaphylaxis*		
Nervous system disorders		Dysgeusia[a] Headache[a]				
Vascular disorders			Hypertension*			
Gastrointestinal disorders		Diarrhoea[a] Nausea*	Vomiting[a] Abdominal pain*			
Skin and subcutaneous tissue disorders				Toxic epidermal necrolysis* Stevens-Johnson syndrome*		
General disorders and administration site conditions				Malaise*		

* Adverse drug reaction identified post-marketing.

a. Occurring at a ≥1% frequency in the PAXLOVID group and at a greater frequency than in the placebo group and/or likely associated with PAXLOVID based on available data and causality assessment.

b. Frequency cannot be estimated from the available data.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nsp5 protease. Inhibition of SARS-CoV-2 M^{pro} renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Nirmatrelvir was shown to be an inhibitor of SARS-CoV-2 M^{pro} (Ki=3.1 nM, or IC_{50}=19.2 nM) in a biochemical enzymatic assay. Nirmatrelvir was found to bind directly to the SARS-CoV-2 M^{pro} active site by X-ray crystallography.

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 differentiated normal human bronchial epithelial (dNHBE) cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure.

Nirmatrelvir had similar cell culture antiviral activity (EC_{50} values in the low nanomolar range ≤1.1-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.1.621.1) and Omicron (B.1.1.529/BA.1) variants assessed in Vero E6 P-gp knockout cells. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 3.7-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7 (P252L+F294L), BF.7 (T243I), BQ.1.11, BQ.1, XBB.1.5, EG.5 and JN.1 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 88 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.8 relative to the USA-WA1/2020 isolate.

Nirmatrelvir showed antiviral activity in different assays than those used for the other variants of concern against the Omicron variant with IC_{50} values of 70 nM and 23 nM in the HeLa-ACE2 and Vero-TMPRSS cells compared to the SARS-CoV-2 USA-WA1/2020 strain which had IC_{50} values of 207 nM and 38 nM in the same cell lines, respectively, using an immunostaining-based method.

Antiviral resistance in cell culture and biochemical assays

SARS-CoV-2 M^{pro} residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with M^{pro} substitutions, and biochemical assays with recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions. Table 7 indicates M^{pro} substitutions and combinations of M^{pro} substitutions that have been observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual M^{pro} substitutions are listed regardless of whether they occurred alone or in combination

with other M^{pro} substitutions. Note that the M^{pro} S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of M^{pro}. Substitutions at other M^{pro} cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

Table 7: SARS-CoV-2 M^{pro} amino acid substitutions selected by nirmatrelvir in cell culture

Single substitution (EC_{50} value fold change)	T21I (1.1-4.8), L50F (1.5-4.2), F140L (4.1), S144A (2.2-5.3), E166A (3.3), E166V (25-288), A173V (0.9-1.7), P252L (5.9), and T304I (1.4-5.5).
≥2 substitutions (EC_{50} value fold change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1-8.9), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

In a biochemical assay using recombinant SARS-CoV-2 M^{pro} containing amino acid substitutions, the following SARS-CoV-2 M^{pro} substitutions led to ≥3-fold reduced activity (fold change based on Ki values) of nirmatrelvir: Y54A (25), F140A (21), F140L (7.6), F140S (230), G143S (3.6), S144A (46), S144E (480), S144T (170), H164N (6.7), E166A (35), E166G (6.2), E166V (7,700), P168del (9.3), H172Y (250), A173S (4.1), A173V (16), R188G (38), Q192L (29), Q192P (7.8), and V297A (3.0). In addition, the following combinations of M^{pro} substitutions led to ≥3-fold reduced nirmatrelvir activity: T21I+S144A (20), T21I+E166V (11,000), T21I+A173V (15), L50F+E166V (4,500), E55L+S144A (56), T135I+T304I (5.1), F140L+A173V (95), S144A+T304I (28), E166V+L232R (5,700), P168del+A173V (170), H172Y+P252L (180), A173V+T304I (28), T21I+S144A+T304I (51), T21I+A173V+T304I (55), L50F+E166A+L167F (180), T21I+L50F+A193P+S301P (7.3), L50F+F140L+L167F+T304I (190), and T21I+C160F+A173V+V186A+T304I (28). The following substitutions and substitution combinations emerged in cell culture but conferred <3-fold reduced nirmatrelvir activity in biochemical assays: T21I (1.6), L50F (0.2), P108S (2.9), T135I (2.2), C160F (0.6), L167F (1.5), T169I (1.4), V186A (0.8), A191V (0.8), A193P (0.9), P252L (0.9), S301P (0.2), T304I (1.0), T21I+T304I (1.8), and L50F+T304I (1.3). The clinical significance of these substitutions is unknown.

Most single and some double M^{pro} amino acid substitutions identified which reduced the susceptibility of SARS-CoV-2 to nirmatrelvir resulted in an EC_{50} shift of <5-fold compared to wild type SARS-CoV-2. Virus containing E166V, which confers high resistance, appears to have replication defect since it either could not be generated or had a very low virus titre although double mutants E166V + T21I or L50F replicated well with growth kinetics similar to WT. Both T21I and L50F rescued the replication defect conferred by E166V and double mutants T21I+E166V and L50F+E166V, as well as E166V, are highly resistant to nirmatrelvir. In general, triple and some double M^{pro} amino acid substitutions led to EC_{50} changes of >5-fold to that of wild type. The clinical significance needs to be further understood, particularly in the context of nirmatrelvir high clinical exposure (≥5× EC_{90}). Thus far, these substitutions have not been identified as treatment-emergent substitutions associated hospitalisation from the EPIC-HR or the EPIC-SR studies.

Treatment-emergent substitutions were evaluated among participants in clinical trials EPIC-HR/SR with sequence data available at both baseline and a post-baseline visit (n=907 PAXLOVID-treated participants, n=946 placebo-treated participants). SARS-CoV-2 M^{pro} amino acid changes were classified as PAXLOVID treatment-emergent substitutions if they were absent at baseline, occurred at the same amino acid position in 3 or more PAXLOVID -treated participants and were ≥2.5-fold

more common in PAXLOVID-treated participants than placebo-treated participants post-dose. The following PAXLOVID treatment-emergent M^{pro} substitutions were observed: T98I/R/del (n=4), E166V (n=3), and W207L/R/del (n=4). Within the M^{pro} cleavage sites, the following PAXLOVID treatment-emergent substitutions were observed: A5328S/V (n=7) and S6799A/P/Y (n=4). These cleavage site substitutions were not associated with the co-occurrence of any specific M^{pro} substitutions.

None of the treatment-emergent substitutions listed above in M^{pro} or M^{pro} cleavage sites occurred in PAXLOVID-treated participants who experienced hospitalisation. Thus, the clinical significance of these substitutions is unknown.

Viral load rebound

Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e. viral RNA rebound) in nasopharyngeal samples were observed on Day 10 and/or Day 14 in both nirmatrelvir-ritonavir and placebo recipients in the EPIC-HR and EPIC-SR studies. Viral RNA rebound was detected in 4.2% (36 of 852) of placebo participants and 6.3% (54 of 862) of nirmatrelvir-ritonavir participants in the EPIC-HR study. In the EPIC-SR study, viral RNA rebound was detected in 4.6% (27 of 584) of placebo participants and 5.5% (33 of 599) of nirmatrelvir-ritonavir participants. The results of EPIC-HR and EPIC-SR do not suggest an association between viral RNA rebound and COVID-19 related hospitalisation or death from any cause. The clinical relevance of viral RNA rebound following PAXLOVID or placebo remains unclear.

Cross-resistance

Cross-resistance is not expected between nirmatrelvir and remdesivir or any other anti-SARS-CoV-2 agents with different mechanisms of action (i.e., agents that are not M^{pro} inhibitors).

Pharmacodynamic effects

Cardiac electrophysiology

At 3 times the steady state peak plasma concentration (C_{max}) at the recommended dose, nirmatrelvir does not prolong the QTc interval to any clinically relevant extent.

Effects on viral RNA levels

Changes in viral RNA levels in nasopharyngeal samples from baseline to Day 5 were evaluated in 1,359 participants who had a detectable nasal viral load by RT-PCR at baseline in EPIC-HR, and 971 participants in EPIC-SR. In EPIC-HR and EPIC-SR the mean viral load reduction in PAXLOVID recipients relative to placebo was -0.777 $\log_{10}$ copies/mL (95% CI: -0.937, -0.617) and -0.868 $\log_{10}$ copies/mL (95% CI: -1.073, -0.663), respectively.

Clinical trials

Efficacy in participants at high risk of progressing to severe COVID-19 illness (EPIC-HR)

The efficacy of PAXLOVID is based on the analysis of EPIC-HR, a Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised symptomatic adult participants with a confirmed diagnosis of SARS-CoV-2 infection.

Eligible participants were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI > 25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, diabetes, sickle cell disease, neurodevelopmental

disorders, active cancer or medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. The study excluded individuals with a known history of prior COVID-19 infection or vaccination. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study.

Participants were randomised (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The primary efficacy endpoint is the proportion of participants with COVID-19 related hospitalisation or death from any cause through Day 28. Time to sustained alleviation and sustained resolution of all targeted symptoms through Day 28 were key secondary efficacy endpoints. These analyses were conducted in the modified intent-to-treat (mITT) analysis set (all treated participants with onset of symptoms ≤ 3 days at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment, the mITT1 analysis set (all treated subjects with onset of symptoms ≤ 5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,213 participants were randomised to receive either PAXLOVID or placebo. At baseline, mean age was 45 years with 51% were male; 71% were White, 4% were Black or African American, and 15% were Asian; 41% were Hispanic or Latino; 67% of subjects had onset of symptoms ≤3 days before initiation of study treatment; 49% of subjects were serological negative at baseline; the mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/mL (2.89); 27% of subjects had a baseline viral load of ≥7 $\log_{10}$ copies/mL; 6% of participants either received or were expected to receive COVID-19 therapeutic mAb treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses.

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

At the primary completion date (PCD) analysis, 697 (62.2%) participants in the PAXLOVID group and 682 (60.6%) participants in the placebo group were included in the mITT analysis set. The event rate of a COVID-19-related hospitalisation or death from any cause through Day 28 in the mITT analysis set in participants who received treatment within 3 days of symptom onset was 44/682 (6.45%) in the placebo group, and 5/697 (0.72%) in the PAXLOVID group. The PAXLOVID group showed a 5.81% (95% CI: -7.78% to -3.84; p<0.0001) absolute reduction, or 88.9% relative reduction in primary endpoint events compared to placebo. No deaths were reported in the PAXLOVID group compared with 9 deaths in the placebo group.

Table 8 provides results of the primary endpoint in mITT1 analysis population demonstrating superiority of PAXLOVID compared to placebo for COVID-19 related hospitalisation or death from any cause through Day 28. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 86% (95% CI: 73%, 93%).

Table 8: Efficacy Results in Non-Hospitalised Adults with COVID-19 Dosed within 5 Days of Symptom Onset who Did not Receive COVID-19 mAb Treatment at Baseline (mITT1 Analysis Set)

	PAXLOVID (N=977)	**Placebo (N=989)**
COVID-19 related hospitalisation or death from any cause through Day 28		
n (%)	9 (0.9%)	64 (6.5%)
Reduction relative to placebo[a] (95% CI), %	-5.64 (-7.31, -3.97)	
p-value	<0.0001	
All-cause mortality through Day 28, %	0	12 (1.2%)

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days after COVID-19 symptom onset).

The determination of primary efficacy was based on a planned interim analysis of 754 subjects in mITT population. The estimated risk reduction was -6.5% with a 95% CI of (-9.3%, -3.7%) and 2-sided p-value <0.0001.

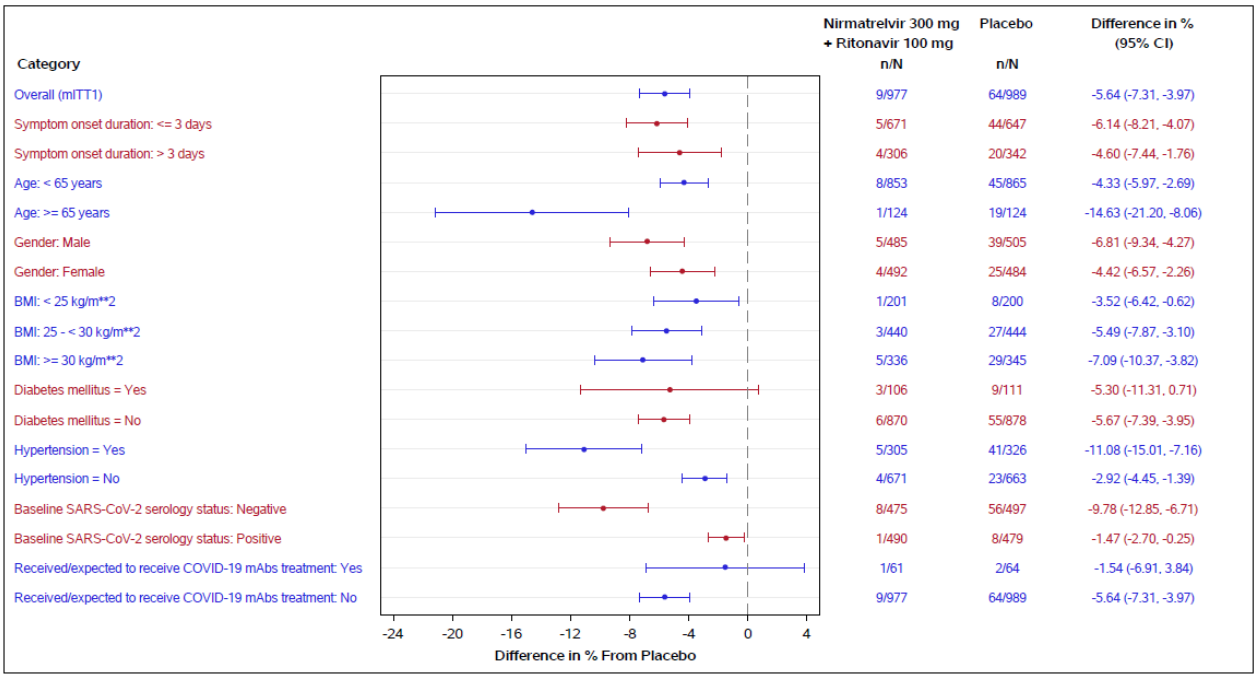
For the secondary endpoint of all-cause mortality through Week 24, there were 0 and 15 (1.5%) events in the PAXLOVID arm and placebo arm, respectively.

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

Consistent results were observed in the mITT and mITT2 analysis populations. A total of 1318 subjects were included in the mITT analysis population. The event rates were 5/671 (0.75%) in the PAXLOVID group, and 44/647 (6.80%) in the placebo group.

Similar trends have been observed across subgroups of participants (see Figure 1). These subgroup analyses are considered exploratory.

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



Abbreviations: BMI=body mass index, COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibodies; mITT1=modified intent-to-treat 1 (all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days after COVID-19 symptom onset); N=number of participants in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti-SARS-CoV-2 S or Elecsys anti-SARS-CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on Normal approximation of the data are presented.

Participants performed daily self-assessments of COVID-19 associated symptoms of cough, shortness of breath or difficulty breathing, feeling feverish, chills or shivering, muscle or body aches, diarrhoea, nausea, vomiting, headache, sore throat, stuffy or runny nose. The severity of each symptom was rated as absent, mild, moderate, or severe. Sustained symptom alleviation was defined as the first of 4 consecutive days when all of the above symptoms scored as moderate or severe at study entry were scored as mild or absent, and all of the above symptoms scored mild or absent at study entry were scored as absent. Sustained symptom resolution was defined as the time when all of the above symptoms were scored as absent for 4 consecutive days. Table 9 displays the results for time to sustained symptom alleviation and sustained symptom resolution in the mITT1 population. The PAXLOVID group demonstrated superiority to the placebo group in both analyses.

Table 9:Analyses of Time to Sustained Symptom Alleviation and Sustained Symptom Resolution Through 28 Days (mITT1 Analysis Set): EPIC-HR

	PAXLOVID (N=970)	Placebo (N=986)
Time to sustained symptom alleviation (days)[a]		
Median	13	15
HR vs placebo (95% CI)[b]	1.266 (1.134, 1.412)	
p-value	<0.0001	
Time to sustained symptom resolution (days)[a]		
Median	16	19
HR vs placebo (95% CI)[b]	1.200 (1.068, 1.348)	
p-value	0.0022	

Abbreviations: CI=confidence interval; HR=hazard ratio; COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT1=modified intent-to-treat 1 (all participants randomly assigned to study intervention, who took at least 1 dose of study intervention, with at least 1 post-baseline visit through Day 28, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤5 days after COVID-19 symptom onset); SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

a. Participants who were hospitalised for the treatment of COVID-19 or died during the 28-day period were considered as not achieving sustained symptom alleviation or resolution.

b. Evaluation was done in a Cox proportional hazard model with treatment and geographic region effects as independent variables, and symptom onset duration (≤3, >3 days), baseline SARS-CoV-2 serology status and baseline viral load (<4, ≥4 $\log_{10}$ copies/mL) as covariates.

The proportion of participants with any severe COVID-19 associated symptom was 22% in the PAXLOVID group and 19% in the placebo group at baseline (Day 1), 17% and 18%, respectively, during treatment (from Day 2 to Day 6), and 8% and 11%, respectively, after treatment (from Day 7 to Day 28).

Efficacy in vaccinated participants with at least 1 risk factor for progression to severe COVID 19 illness (EPIC-SR)

EPIC-SR was a Phase 2/3, randomised, double-blind, placebo-controlled trial in non-hospitalised symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects were 18 years of age or older with COVID-19 symptom onset of ≤5 days who were at standard risk for progression to severe disease. The trial included previously unvaccinated subjects with no risk factors for progression to severe disease or subjects fully vaccinated against COVID-19 (i.e., completed a primary vaccination series) with at least 1 of the risk factors for progression to severe disease as defined in EPIC-HR. A total of 1,296 subjects were randomised (1:1) to receive PAXLOVID or placebo orally every 12 hours for 5 days; of these, 49% were fully vaccinated with at least 1 risk factor for progression to severe disease.

The primary endpoint in this trial, the difference in time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 among PAXLOVID versus placebo recipients, was not met.

In an exploratory analysis of the subgroup of fully vaccinated subjects with at least 1 risk factor for progression to severe disease, a non-statistically significant numerical reduction (3/317 (0.9%)

PAXLOVID recipients versus 7/314 (2.2%) placebo recipients) relative to placebo for the secondary endpoint of COVID-19 related hospitalisation or death from any cause through Day 28 was observed.

Post-exposure prophylaxis (EPIC-PEP)

EPIC-PEP was a phase 2/3, randomised, double-blind, double-dummy, placebo-controlled study assessing the efficacy of PAXLOVID (administered 5 days or 10 days) in post-exposure prophylaxis of COVID-19 in household contacts of symptomatic individuals infected with SARS-CoV-2. Eligible participants were asymptomatic adults 18 years of age and older who were SARS-CoV-2 negative at screening and who lived in the same household with symptomatic individuals with a recent diagnosis of SARS-CoV-2. A total of 2,736 participants were randomised (1:1:1) to receive PAXLOVID orally every 12 hours for 5 days, PAXLOVID orally every 12 hours for 10 days, or placebo.

The results of the primary endpoint for EPIC-PEP are presented in Table 10.

Table 10: Efficacy results in symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection and symptomatic or asymptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection in participants exposed to SARS-CoV-2 through household contact (mITT analysis set)

	PAXLOVID		
	5 Days (N=844)	**10 Days (N=830)**	**Placebo (N=840)**
Symptomatic, RT-PCR or RAT Confirmed SARS-CoV-2 Infection Through Day 14			
n (%)	22 (2.6%)	20 (2.4%)	33 (3.9%)
Relative risk reduction vs placebo (95% CI)	0.298 (-0.167, 0.578)	0.355 (-0.115, 0.627)	
p-value	0.1722	0.1163	

Abbreviations: CI=confidence interval; mITT=all participants randomised to study intervention who took at least 1 dose of study intervention and had a negative RT-PCR result at baseline; RAT=rapid antigen test; RT-PCR=reverse transcriptase–polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

5.2 Pharmacokinetic properties

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in healthy participants and in participants with mild to moderate COVID-19.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic (PK) enhancer resulting in higher systemic concentrations and longer half-life 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 as oral suspension formulation 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 µg/mL (25%) and 27.6 µg*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}) 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 increased the exposure of nirmatrelvir (approximately 61% increase in mean C_{max} and 20% increase in mean AUC_{last}) relative to fasting conditions following administration of 300 mg nirmatrelvir (2 × 150 mg)/100 mg ritonavir tablets.

Distribution

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

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

Metabolism

Nirmatrelvir

In vitro studies assessing nirmatrelvir without concomitant ritonavir suggest that nirmatrelvir is primarily metabolised by CYP3A4. 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.

Ritonavir

Nearly all of the plasma radiolabel after a single oral 600 mg dose of radiolabelled ritonavir was attributed to unchanged ritonavir. Four ritonavir metabolites have been identified in man. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite. The AUC of the M-2 metabolite was approximately 3% of the AUC of parent drug. Studies utilising human liver microsomes have demonstrated that CYP3A4 is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formulation of M-2. The metabolites are principally eliminated in the faeces.

Excretion

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.

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

An open-label study compared nirmatrelvir/ritonavir pharmacokinetics in healthy adult subjects and subjects with mild (eGFR ≥60 to <90 mL/min/1.73m^2), moderate (eGFR ≥30 to <60 mL/min/1.73m^2), and severe (eGFR <30 mL/min/1.73m^2) renal impairment following administration of a single oral dose of nirmatrelvir 100 mg enhanced with ritonavir 100 mg administered at -12, 0, 12, and 24 hours. 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. See Table below.

Table 11: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Renal Function (n=8)	**Mild Renal Impairment (n=8)**	**Moderate Renal Impairment (n=8)**	**Severe Renal Impairment (n=8)**
C_{max} (µg/mL)	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
AUC_{inf} (µg*hr/mL)	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
T_{max} (hr)	2.0 (1.0 – 4.0)	2.0 (1.0 – 3.0)	2.50 (1.0 – 6.0)	3.0 (1.0 – 6.1)
$T_{1/2}$ (hr)	7.73 ± 1.82	6.60 ± 1.53	9.95 ± 3.42	13.37 ± 3.32

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Patients with severe renal impairment including those requiring haemodialysis

The pharmacokinetics of nirmatrelvir in participants with mild-to-moderate COVID-19 and severe renal impairment (eGFR<30 mL/min/1.73m^2) either requiring haemodialysis (n=12) or not requiring haemodialysis (n=2) were evaluated after administration of 300 mg/100 mg nirmatrelvir/ritonavir once on Day 1 followed by 150 mg/100 mg nirmatrelvir/ritonavir once daily on Days 2-5 for a total of 5 doses.

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

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

Patients with hepatic impairment

A single oral dose of 100 mg nirmatrelvir enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours and 24 hours in subjects with moderate hepatic impairment resulted in similar exposures compared to subjects with normal hepatic function (See Table below).

The pharmacokinetics of nirmatrelvir/ritonavir have not been evaluated in patients with severe hepatic impairment.

Table 12: Impact of Hepatic Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

	Normal Hepatic Function (n=8)	**Moderate Hepatic Impairment (n=8)**
C_{max} (µg/mL)	1.89 (20)	1.92 (48)
AUC_{inf} (µg*hr/mL)	15.24 (36)	15.06 (43)
T_{max} (hr)	2.0 (0.6 – 2.1)	1.5 (1.0 – 2.0)
$T_{1/2}$ (hr)	7.21 ± 2.10	5.45 ± 1.57

Values are presented as geometric mean (geometric % CV) except median (range) for T_{max} and arithmetic mean ± SD for $t_{1/2}$.

Drug 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 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 PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarised in the table below (effect of other medicinal products on nirmatrelvir).

Table 13: Interactions with other Medicines: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the co-administered medicines

	Dose (schedule)			**Percent ratio (in combination with co-administered medicine/ alone) of nirmatrelvir[a] PK parameters (90% CI); no effect=100**	
Co-administered medicine	**Co-administered**	**Nirmatrelvir/ ritonavir**	**N**	**C_{max}**	**AUC[b]**
Carbamazepine[c]	300 mg twice daily (16 doses)	300 mg/ 100 mg once daily (2 doses)	10	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}= observed maximum plasma concentrations; PK=pharmacokinetic.

a. Percent ratio of test (i.e., carbamazepine or itraconazole in combination with nirmatrelvir/ritonavir)/reference (i.e., nirmatrelvir/ritonavir alone).

b. For carbamazepine, AUC=AUC_{inf}, for itraconazole, AUC=AUC_{tau}.

c. 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 midazolam (CYP3A4 substrate), dabigatran (P-gp substrate), or rosuvastatin (OATP1B1 substrate) on the midazolam, dabigatran, and rosuvastatin AUC_{inf} and C_{max}, respectively, are summarised in Table 14.

Table 14: Effect of nirmatrelvir/ritonavir on pharmacokinetics of co-administered drug

Co-administered drug	Dose (schedule)		N	Percent ratio[a] of test/reference of geometric means (90% CI); no effect=100	
	Co-administered	Nirmatrelvir/ ritonavir		C_{max}	AUC_{inf}
Midazolam[b]	2 mg (1 dose)	300 mg/100 mg twice daily (9 doses)	10	368.33 (318.91, 425.41)	1430.02 (1204.54, 1697.71)
Dabigatran[b]	75 mg (1 dose)	300 mg/100 mg twice daily (3 doses)	24	233.06 (172.14, 315.54)	194.47 (155.29, 243.55)
Rosuvastatin[b]	10 mg (1 dose)	300 mg/100 mg twice daily (3 doses)	12	212.44 (174.31, 258.90)	131.18 (115.89, 148.48)

Abbreviations: AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum plasma concentrations; CYP3A4=cytochrome P450 3A4; OATP1B1=organic anion transporting polypeptide 1B1; P-gp=p-glycoprotein.

a. Percent ratio of test (i.e., midazolam, dabigatran, or rosuvastatin in combination with nirmatrelvir/ritonavir)/reference (i.e., midazolam, dabigatran, or rosuvastatin alone).

b. 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. For rosuvastatin, Test=nirmatrelvir/ritonavir plus rosuvastatin, Reference=rosuvastatin. Rosuvastatin is an index substrate for OATP1B1.

5.3 Preclinical safety data

No nonclinical safety studies have been conducted with nirmatrelvir in combination with ritonavir. Complete nonclinical development program was conducted on the individual entities (nirmatrelvir and ritonavir) and no nonclinical combination toxicity studies were performed.

Genotoxicity

PAXLOVID has not been evaluated for the potential to cause genotoxicity.

Nirmatrelvir

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

Ritonavir showed no mutagenic potential in a series of assays for gene mutations (*S. typhimurium, E. coli* and mouse lymphoma cells) and chromosomal damage (mouse micronucleus assay *in-vivo* and human lymphocytes *in-vitro*.

Carcinogenicity

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

Nirmatrelvir

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

Ritonavir

Two-year carcinogenicity studies have been conducted in rodents, at ritonavir dietary levels of 50, 100 and 200 mg/kg/day in mice, and 7, 15 and 30 mg/kg/day in rats. In male mice there was a dose dependent increase in the incidence of hepatocellular adenomas, and adenomas and carcinomas combined, both reaching statistical significance only at the high-dose. In female mice there were small, statistically significant increases in these tumour incidences only at the high-dose. In rats, there were no tumorigenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nirmatrelvir

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Colloidal anhydrous silica
Sodium stearylfumarate.

Film coat
Opadry Complete Film Coating System 05B140011 Pink.

Ritonavir

Tablet core
Copovidone
Calcium hydrogen phosphate
Sorbitan monolaurate
Colloidal anhydrous silica
Sodium stearylfumarate.

Film coating
Hypromellose
Titanium dioxide

Macrogol 400
Hyprolose
Purified talc
Macrogol 3350
Colloidal anhydrous silica
Polysorbate 80.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PAXLOVID is supplied in a carton containing five PA/Al/PVC/Al blister cards marked as "Morning Dose" and "Evening Dose" for tablets to be taken each morning and each evening. PAXLOVID is available in the following pack sizes:

Dose Pack	**Content**
For patients with no dose adjustment: **300 mg nirmatrelvir (as two 150 mg tablets);** **100 mg ritonavir**	**Each Carton Contains:** 30 tablets divided in 5 daily-dose blister cards.
	Each Blister Card Contains: Four nirmatrelvir 150 mg tablets and two ritonavir 100 mg tablets.
For patients with renal impairment: **150 mg nirmatrelvir;** **100 mg ritonavir**	**Each Carton Contains:** 20 tablets divided in 5 daily-dose blister cards.
	Each Blister Card Contains: Two nirmatrelvir 150 mg tablets and two ritonavir 100 mg tablets.

The dose in renal impairment may differ to that indicated by the blister card design. See Section 4.2 Dose and method of administration.

Not all pack sizes may be marketed.

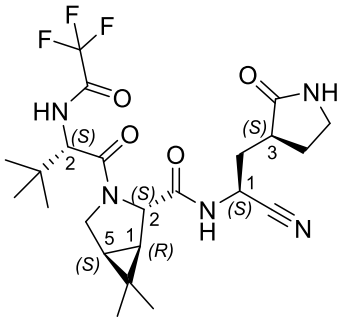
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Nirmatrelvir

Chemical structure



Chemical Name: (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2-oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide.

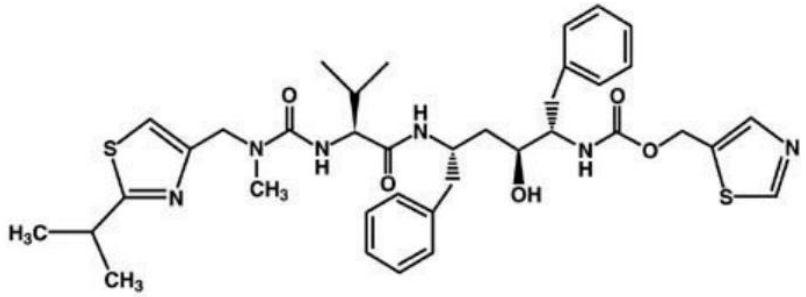
The molecular formula is $C_{23}H_{32}F_3N_5O_4$ and the molecular weight is 499.54.

CAS number

2628280-40-8

Ritonavir

Chemical structure



Chemical Name: 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)].

The molecular formula is $C_{37}H_{48}N_6O_5S_2$ and the molecular weight is 720.95.

CAS number

155213-67-5

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000.

Toll Free Number: 1800 675 229.
www.pfizermedicalinformation.com.au
www.pfizer.com.au.

9. DATE OF FIRST APPROVAL

20 January 2022

10. DATE OF REVISION

13 April 2026

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.2, 4.3, 4.4, 4.8, 5.2 and 6.5	Introduction of dosage adjustment recommendation for severe renal impairment
4.5	Drug interactions section updated to include rimegepant and buspirone.
5.1	Updates to antiviral activity information for EG.5 and JN.1 variants