NEW ZEALAND DATA SHEET

1. PRODUCT NAME

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.

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 coated, oval tablets marked with the Abbott logo and "NK".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Dose

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. 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. The tablets should be swallowed whole and not chewed, broken, or crushed.

Dose Adjustments

Special populations

Renal Impairment

Mild (≥60 to <90 mL/min)

No dose adjustment is needed in patients with mild renal impairment.

Moderate (≥30 to <60 mL/min)

In patients with moderate renal impairment, the dose of PAXLOVID should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg every 12 hours for 5 days to avoid increased toxicity due to over-exposure (this dose adjustment has not been clinically tested).

Note: The daily blister contains two separated parts each containing 2 tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose.

Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours.

Severe (<30 mL/min)

Appropriate dose for patients with severe renal impairment has not yet been determined. PAXLOVID is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined (see Section 4.3 Contraindications).

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 severe hepatic impairment (Child-Pugh Class C), therefore, PAXLOVID is contraindicated in patients with severe hepatic impairment (see Sections 4.3 Contraindications and 5.2 Pharmacokinetic properties).

Paediatric population

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

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 renal impairment.

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).

Table 1: 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	
Antianginal	ranolazine
Antiarrhythmics	amiodarone, flecainide, propafenone
Antibiotic	fusidic acid
Anticancer	neratinib, venetoclax
Anti-gout	colchicine
Antipsychotics	clozapine
Ergot derivatives	ergometrine
Lipid-modifying agents HMG-CoA reductase inhibitors	simvastatin
Opioid analgesic	pethidine
PDE5 inhibitor	avanafil, sildenafil, vardenafil, tadalafil
Sedative/hypnotics	diazepam

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

Interactions that result in decrease in nirmatrelvir/ritonavir concentrations	
Anticancer	apalutamide
Anticonvulsant	carbamazepine[a], phenobarbital, phenytoin
Antimycobacterials	rifampicin
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.

See Table 1 for medicinal products that are contraindicated for concomitant use with PAXLOVID (see Section 4.3 Contraindications) and Table 2 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.

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 renal impairment the dose of PAXLOVID should be reduced. (See Section 4.2 Dose and method of administration, Renal impairment). PAXLOVID is contraindicated in patients with severe renal impairment (See Section 4.3 Contraindications).

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 data sheet for each of these drugs.

4.5 Interaction with other medicines and other forms of interaction

PAXLOVID (nirmatrelvir/ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when co-administered with nirmatrelvir/ritonavir. Thus, co-administration of nirmatrelvir/ritonavir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see Table 1, Section 4.3 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, MATE2K, OAT1, OAT3, OATP1B3, OCT1 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1 (P-gp), MATE1 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 > 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 2).

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

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

Table 3: Established and potentially significant interactions with other medicines

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Analgesics	pethidine	↑ pethidine	Co-administration contraindicated due to potential for serious respiratory depression or haematologic abnormalities (see Section 4.3 Contraindications).
	fentanyl	↑ fentanyl	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with PAXLOVID.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions (see Section 4.3 Contraindications).
Antiarrhythmics	amiodarone, flecainide, propafenone	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias (see Section 4.3 Contraindications).
Antiarrhythmics	lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	apalutamide	↓ 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
	afatinib	↑ afatinib	Caution should be exercised when afatinib is coadministered with PAXLOVID (refer to the afatinib Data Sheet).
	dasatinib, ibrutinib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	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 Data Sheet for anticancer drugs.
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. Avoid concomitant use.
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin	↓ nirmatrelvir/ ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and possible resistance (see Section 4.3 Contraindications).
	lamotrigine	↓ lamotrigine	Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are co-administered with ritonavir.
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.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antifungals	voriconazole, ketoconazole, isavuconazonium sulfate, itraconazole[a]	↓ voriconazole ↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ ritonavir	Avoid concomitant use of voriconazole. Refer to ketoconazole, isavuconazonium sulfate, and itraconazole Data Sheet 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,	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' Data Sheet. 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).
Anti-HIV	efavirenz, nevirapine, raltegravir, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs' Data Sheet.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
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 Data Sheet 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).
Antimycobacterial	rifabutin, bedaquiline	↑ rifabutin ↑ bedaquiline	Refer to rifabutin Data Sheet for further information on rifabutin dose reduction.
	fusidic acid	↑ fusidic acid	Co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated.
Antipsychotics	clozapine	↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias (see Section 4.3 Contraindications).

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine Data Sheet for recommendations.
	haloperidol, risperidone	↑ haloperidol ↑ risperidone	Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nifedipine	↑ 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 individual Data Sheet 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 Data Sheet for further information.
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan Data Sheet for further information.
Ergot derivatives	ergometrine	↑ ergometrine	Co-administration of ergometrine with PAXLOVID is contraindicated (see Section 4.3 Contraindications).

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Hepatitis C direct acting antivirals	glecaprevir/ pibrentasvir	↑ antiviral	It is not recommended to co-administer ritonavir with glecaprevir/pibrentasvir. 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).
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.
	atorvastatin, rosuvastatin	↑ 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.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Immunosuppressants	ciclosporin, tacrolimus, sirolimus, everolimus	↑ ciclosporin ↑ tacrolimus ↑ sirolimus ↑everolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and PAXLOVID. If co-administered, refer to individual Data Sheet for immunosuppressant for further information.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.
PDE5 inhibitor	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).
	avanafil, tadalafil, vardenafil	↑ avanafil ↑ tadalafil ↑ vardenafil	Concomitant use with PAXLOVID is contraindicated (see section 4.3 Contraindications).
Sedative/hypnotics	midazolam[a] (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

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			for midazolam should be considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam Data Sheet for further information.
	diazepam	↑ diazepam	Co-administration diazepam with ritonavir is contraindicated (see section 4.3 Contraindications)
Smoking cessation	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
Systemic corticosteroids	betamethasone, budesonide, dexamethasone, methylprednisolone, prednisone, triamcinolone	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.

a. See Section 5.2 Pharmacokinetics, Drug Interaction Studies Conducted with Nirmatrelvir and Ritonavir.

4.6 Fertility, pregnancy and lactation

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 7 times the human exposure based on unbound 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 rat

Pregnancy – Category B3

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

There are no 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. There was no nirmatrelvir-related effect on rat embryo-fetal development up to the highest dose of 1,000 mg/kg/day (12 times the human exposure based on unbound 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 (25 times the human exposure based on unbound 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 (10x/2.8x C_{max}/AUC_{24} over the predicted clinical exposure).

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.

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.

Lactation

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production.

Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded.

Breast-feeding should be discontinued during treatment with PAXLOVID and for 7 days after the last dose of PAXLOVID.

4.7 Effects on ability to drive and use machinery

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 Undesirable effects

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 Pharmacodynamic properties, Clinical trials). A total of 2,224 symptomatic adult subjects 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either PAXLOVID (n=1,109) or placebo (n=1,115).

Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. PAXLOVID [300 mg nirmatrelvir with 100 mg ritonavir] or placebo were to be taken twice daily for 5 days.

Adverse events (all grades regardless of causality) in the PAXLOVID group are presented in Table 4. The most commonly reported adverse events reported during treatment with PAXLOVID and through day 34 after initiating study treatment were dysgeusia, diarrhoea, headache and vomiting. Also refer to Table 5. The proportions of subjects who discontinued treatment due to an adverse event were 23 (2.1%) in the PAXLOVID group and 47 (4.2%) in the placebo group. The proportion of subjects with serious adverse events were 18 (1.6%) and 74 (6.6%) in the PAXLOVID group and in the placebo group, respectively.

Table 4: Summary of Treatment-Emergent Adverse Events (All Causalities) Reported by ≥1% Patients in the Treatment Group or with ≥5 Subject Difference in Incidence or at Greater Frequency in the Treatment Group than the Placebo Group

	Nirmatrelvir 300 mg/ Ritonavir 100 mg n (%)	**Placebo n (%)**
Number of Participants	**n=1109**	**n=1115**
Participants with events	251 (22.6)	266 (23.9)
Gastrointestinal disorders		
Diarrhoea	34 (3.1)	18 (1.6)
Vomiting	12 (1.1)	9 (0.8)
Vascular disorders		
Hypertension	7 (0.6)	2 (0.2)
Musculoskeletal and connective tissue disorders		
Myalgia	7 (0.6)	2 (0.2)
Nervous System disorders		
Dysgeusia	62 (5.6)	3 (0.3)
Headache	15 (1.4)	14 (1.3)

The adverse 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 5: Frequency of Adverse Reactions by System Organ Class Reported by ≥1% Patients in the Treatment Group or with ≥5 Subject Difference in Incidence or at a Greater Frequency than the Placebo Group

System organ class	Frequency category	Adverse reactions
Gastrointestinal disorders	Common	Diarrhoea, Vomiting
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
Nervous system disorders	Common	Dysgeusia, Headache
Vascular disorders	Uncommon	Hypertension

Post-marketing experience

Immune system disorders: Hypersensitivity

Reporting of suspected adverse reactions

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 https://nzphvc.otago.ac.nz/reporting/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.

Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro

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 Mpro (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 Mpro active site by X-ray crystallography.

Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

Antiviral activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{50} value of 61.8 nM and EC_{90} value of 181 nM) after 3 days of drug exposure. Nirmatrelvir had cell culture antiviral activity using a Vero derived cell line (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 two mouse strains with reduction in lung viral titre and amelioration of disease (weight loss and lung pathology).

Resistance

No information on antiviral resistance is currently available. Studies to evaluate selection of resistance to nirmatrelvir with SARS-CoV-2 in cell culture and clinical studies have not been completed. Only i*n 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. Higher concentration of 50xEC_{50} failed to produce virus.

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% CI for baseline and ritonavir adjusted QTcF estimate was 1.96 ms at approximately 4-fold higher concentration than the mean steady-state peak concentration after a therapeutic dose of nirmatrelvir/ritonavir 300 mg/100 mg.

Clinical efficacy and safety

Clinical trials

Evaluation of Protease Inhibition for COVID-19 - High-Risk Patients (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.

The primary efficacy endpoint is 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 at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody (mAb) treatment, the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days).

A total of 2,246 participants were randomised to receive either PAXLOVID or placebo. At baseline, mean age was 46 years with 51% were male; 72% were White, 5% were Black, and 14% were Asian; 45% were Hispanic or Latino; 66% of subjects had onset of symptoms ≤3 days from initiation of study treatment; 47% of subjects were serological negative at baseline; the mean (SD) baseline viral load was 4.63 $\log_{10}$ copies/mL (2.87); 26% of subjects had a baseline viral load of >10^7 (units); 6% of participants either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses.

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

At 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 6 provides results of the primary endpoint in mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 88% (95% CI: 75%, 94%).

Table 6: Efficacy Results in Non-Hospitalised Adults with COVID-19 Dosed within 5 Days of Symptom Onset who Did not Receive COVID-19 Monoclonal Antibody Treatment at Baseline (mITT1 Analysis Set)

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

Abbreviations: CI=confidence interval.

The determination of primary efficacy was based on a planned interim analysis of 774 subjects in mITT population. The estimated risk reduction was -6.3% with a 95% CI of (-9.0%, -3.6%) and 2-sided p-value <0.0001.

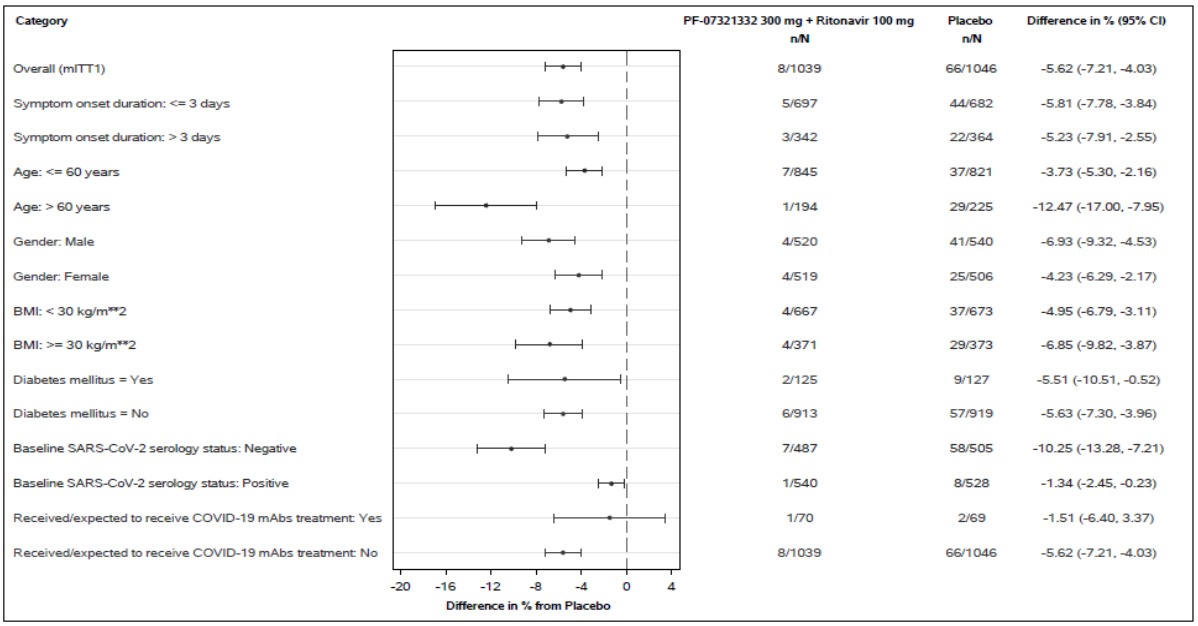
a. The estimated cumulative proportion of participants hospitalised or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Consistent results were observed in the mITT and mITT2 analysis populations. A total of 1,379 subjects were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the PAXLOVID group, and 44/682 (6.45%) in the placebo group. The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I.

Relative to placebo, PAXLOVID 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.

Similar trends have been observed across subgroups of subjects (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: mAb=monoclonal antibodies; 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.

Relative to placebo, PAXLOVID 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.

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 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 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%.

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 radiolabeled 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), moderate (eGFR ≥30 to <60 mL/min), and severe (eGFR <30 mL/min) 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 7: 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 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 8: 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 metabolized 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 9: 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] pharmacokinetic 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 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. 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) or dabigatran (P-gp substrate) on the midazolam and dabigatran AUC and C_{max}, respectively, are summarised in Table 10.

Table 10: 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[b]
Midazolam[c]	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

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 tumourigenic 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

12 months.

6.4 Special precautions for storage

Store below 25 C.

6.5 Nature and contents of container

PAVLOVID is supplied in a carton of 30 tablets in five PA/Al/PVC/Al blister cards marked as “Morning Dose” and “Evening Dose” for tablets to be taken each morning and each evening.

Each blister card contains four nirmatrelvir tablets and two ritonavir tablets.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz
www.pfizer.co.nz

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

02 March 2022

10. DATE OF REVISION OF THE TEXT

07 April 2022

Summary table of changes

Section changed	Summary of new information
4.5, 4.8, 5.1, 5.2, 9	Minor editorial changes.
4.5	Addition of dabigatran as a drug interaction.
4.8	Update to include hypersensitivity as an adverse effect.
5.2	Update to include effect of nirmatrelvir/ritonavir on pharmacokinetics of midazolam and dabigatran.