PAXLOVID

Table of Content

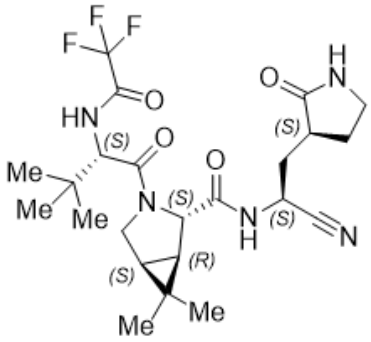
Please click on either of the following links to access the required information:

1. NAME OF THE MEDICINAL PRODUCT

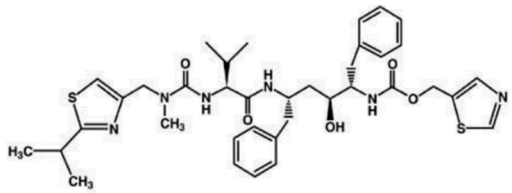
PAXLOVID FILM-COATED TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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



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



3. PHARMACEUTICAL FORM

Nirmatrelvir

Film-coated tablet.

Pink, oval, with a dimension of approximately 17.6 mm in length and 8.6 mm in width debossed with ‘PFE’ on one side and ‘3CL’ on the other side.

Ritonavir

White film-coated ovaloid tablets debossed with [Abbott logo] and the code ‘NK’ on one side;

OR

White film-coated ovaloid tablets debossed with ‘NK’ on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

PAXLOVID is indicated for the treatment of mild-to-moderate Coronavirus Disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

4.2. Posology and method of administration

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.

Posology

The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally twice daily for 5 days. PAXLOVID should be given as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset even if baseline COVID-19 symptoms are mild. If a patient requires hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, it is recommended that the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

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.

Patient selection

The following medical conditions or other factors place adult patients at high risk for progression to severe COVID-19:

- Older age (e.g., 60 years of age and older)
- Obesity or being overweight [e.g., body mass index (BMI) >25 kg/m^2]
- Current smoker
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung disease [e.g., chronic obstructive pulmonary disease, asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension]
- Sickle cell disease

- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Active cancer
- Medical-related technological dependence not related to COVID-19 (e.g., tracheostomy, gastrostomy, or positive pressure ventilation)

Other medical conditions or factors (e.g., race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and are not limited to the medical conditions or factors listed above. Healthcare providers should consider the benefit-risk for an individual patient.

Special populations

Pediatric population
The safety and efficacy of PAXLOVID have not been studied in patients younger than 18 years of age.

Renal impairment
No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥60 to <90 mL/min).

In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dose of PAXLOVID should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg twice daily for 5 days.

Note: The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose. Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours.

PAXLOVID is not recommended 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 5.2).

Hepatic impairment
No dosage adjustment is needed in patients with 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 participants with severe (Child-Pugh Class C) hepatic impairment; therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment (see section 5.2).

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.

Method of administration

For oral use.

PAXLOVID can be taken with or without food (see section 5.2). The tablets should be swallowed whole and not chewed, broken, or crushed.

4.3. Contraindications

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity to the active substances (nirmatrelvir/ritonavir) or to any of the product excipients.

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). 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.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide
- Benign prostatic hyperplasia agents: silodosin
- Cardiovascular agents: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- Immunosuppressants: voclosporin
- Microsomal triglyceride transfer protein inhibitor: lomitapide
- Migraine medications: eletriptan, ubrogepant
- Mineralocorticoid receptor antagonists: finerenone
- Non-opioid analgesic (selective blocker of $Na_v1.8$ sodium channels): suzetrigine
- Opioid antagonists: naloxegol
- PDE5 inhibitor: sildenafil when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam
- Serotonin receptor 1A agonist/serotonin receptor 2A antagonist: flibanserin
- 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).

- Anticancer drugs: apalutamide, enzalutamide
- Anticonvulsant: carbamazepine, phenobarbital, primidone, phenytoin
- Antimycobacterials: rifampin, rifapentine
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St. John's Wort (*Hypericum perforatum*)

4.4. Special warnings and precautions for use

Risk of serious adverse reactions due to drug interactions

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

Initiation of medications 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 1 for drugs that are contraindicated for concomitant use with nirmatrelvir/ritonavir and for potentially significant interactions with other drugs (see section 4.5; also see section 4.3 for drugs that are contraindicated for concomitant use). Potential for drug interactions should be considered prior to and during PAXLOVID therapy; concomitant medications should be reviewed during PAXLOVID therapy and the patient should be monitored 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).

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). 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.

Risk of HIV-1 resistance development

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

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

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 metabolized 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.

Drugs that are extensively metabolized 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 drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see section 4.3).

Co-administration of other CYP3A4 substrates that may lead to potentially significant interaction should be considered only if the benefits outweigh the risks (see Table 1).

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

Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with nirmatrelvir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Table 1: Established and other potentially significant drug interactions

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).
Alpha 1-adrenoreceptor antagonist	tamsulosin	↑ tamsulosin	Avoid concomitant use with PAXLOVID.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			life-threatening reactions (see section 4.3).
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias (see section 4.3).
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).
Anticancer drugs	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib or ivosidenib 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 hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
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 label for further information.

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	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 label for more information.
Anticonvulsants	carbamazepine[a], phenobarbital, phenytoin, primidone	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance (see section 4.3).
Anticonvulsants	clonazepam	↑ anticonvulsant	A dose decrease may be needed for clonazepam when co-administered with PAXLOVID and clinical monitoring is recommended.
Antidepressants	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
	trazodone	↑ trazodone	Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered. Refer to trazadone product label for further information.
Antifungals	voriconazole	↓ voriconazole	Avoid concomitant use of voriconazole.
	ketoconazole, isavuconazonium sulfate, itraconazole[a]	↑ ketoconazole ↑ isavuconazonium sulfate ↑ itraconazole ↑ nirmatrelvir/ritonavir	Refer to ketoconazole, isavuconazonium sulfate, and itraconazole product labels for further information.

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
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).
Anti-HIV protease inhibitors	atazanavir, darunavir, tipranavir	↑ protease inhibitor	For further information, refer to the respective protease inhibitors' prescribing information. Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events (see section 4.2).
Anti-HIV	efavirenz, maraviroc, nevirapine, zidovudine, bictegravir/ emtricitabine/ tenofovir	↑ efavirenz ↑ maraviroc ↑ nevirapine ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information.
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment.
Antimycobacterial	rifampin, rifapentine	↓ 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).
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information. Refer to rifabutin product label for further information on rifabutin dose reduction.

Table 1: Established and other potentially significant drug interactions

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, pimozide	↑ lurasidone ↑ pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias (see section 4.3).
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations.
	clozapine	↑ clozapine	If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions.
Benign prostatic hyperplasia agents	silodosin	↑ silodosin	Co-administration contraindicated due to potential for postural hypotension (see section 4.3).
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, 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 individual product label for

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			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 label for further information.
Cardiovascular agents	eplerenone	↑ eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalemia (see section 4.3).
	ivabradine	↑ ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances (see section 4.3).
Cardiovascular agents	aliskiren, ticagrelor, vorapaxar	↑ aliskiren ↑ ticagrelor ↑ vorapaxar	Avoid concomitant use with PAXLOVID.
	clopidogrel	↓ clopidogrel active metabolite	
	cilostazol	↑ cilostazol	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol product label for more information.
Corticosteroids primarily metabolized 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

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			Cushing's syndrome and adrenal suppression associated with short-term use of a strong CYP3A4 inhibitor is low. Alternative corticosteroids including beclomethasone, prednisone, 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).
Cystic fibrosis transmembrane conductance regulator potentiators	ivacaftor elexacaftor/ tezacaftor/ivacaftor tezacaftor/ivacaftor	↑ ivacaftor ↑ elexacaftor/ tezacaftor/ivacaftor ↑ tezacaftor/ivacaftor	Reduce dosage when co-administered with PAXLOVID. Refer to individual product labels for more information.
Dipeptidyl peptidase 4 (DPP4) inhibitors	saxagliptin	↑ saxagliptin	Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin product label 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 label for further information.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system (see section 4.3).
Hepatitis C direct acting antivirals	elbasvir/grazoprevir, glecaprevir/ pibrentasvir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID.

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	ombitasvir/ paritaprevir/ritonavir and dasabuvir sofosbuvir/ velpatasvir/ voxilaprevir		Refer to the ombitasvir/paritaprevir/ ritonavir and dasabuvir label for further information. Refer to the sofosbuvir/velpatasvir/ voxilaprevir product label 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).
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).
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis (see section 4.3). Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of PAXLOVID, during the 5 days of PAXLOVID treatment and for 5 days after completing PAXLOVID.
HMG-CoA reductase inhibitors	atorvastatin, rosuvastatin[a]	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with PAXLOVID. Atorvastatin and rosuvastatin do not need to be held prior to or after completing PAXLOVID.
Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered during the

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID.
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration contraindicated due to potential for acute and/or chronic nephrotoxicity (see section 4.3).
Immunosuppressants	Calcineurin inhibitors: cyclosporine, tacrolimus mTOR inhibitors: everolimus, sirolimus	 ↑ cyclosporine ↑ tacrolimus ↑ everolimus ↑ sirolimus	Avoid concomitant use of calcineurin inhibitors and mTOR inhibitors during treatment with PAXLOVID. If the co-administration cannot be avoided, 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 label and latest guidelines for further information and obtain expert consultation of a multidisciplinary group (see section 4.4).
Janus kinase (JAK) inhibitors	tofacitinib upadacitinib	↑ tofacitinib ↑ upadacitinib	Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib product label for more information. Dosing recommendations for co-administration of upadacitinib with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib product label for more information.

Table 1: Established and other potentially significant drug interactions

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.
Microsomal triglyceride transfer protein (MTTP) inhibitor	lomitapide	↑ lomitapide	Co-administration contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions (see section 4.3).
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).
	ubrogepant	↑ ubrogepant	Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions (see section 4.3).
Migraine medications	rimegepant	↑ rimegepant	Avoid concomitant use with PAXLOVID.
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia (see section 4.3).
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 label for more information.

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Narcotic analgesics	fentanyl, hydrocodone, oxycodone, meperidine	↑ fentanyl ↑ hydrocodone ↑ oxycodone ↑ meperidine	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl, hydrocodone, oxycodone, or meperidine 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 label for more information.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly.
Neuropsychiatric agents	suvorexant	↑ suvorexant	Avoid concomitant use of suvorexant with PAXLOVID.
	aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, pimavanserin	↑ aripiprazole ↑ brexpiprazole ↑ cariprazine ↑ iloperidone ↑ lumateperone ↑ pimavanserin	Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual product label for more information.
Non-opioid analgesic (selective blocker of $Na_v1.8$ sodium channels)	suzetrigine	↑ suzetrigine and active metabolite M6-SUZ	Co-administration contraindicated due to potential for serious and/or life-threatening suzetrigine adverse reactions (see section 4.3).
Pulmonary hypertension agents (PDE5 inhibitors)	sildenafil	↑ sildenafil	Co-administration of sildenafil with PAXLOVID is contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension,

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			prolonged erection, and syncope (see section 4.3).
Pulmonary hypertension agents (PDE5 inhibitors)	tadalafil	↑ tadalafil	Avoid concomitant use of tadalafil with PAXLOVID.
Pulmonary hypertension agents (sGC stimulators)	riociguat	↑ riociguat	Dosage adjustment is recommended for riociguat. Refer to the riociguat product label for more information.
Erectile dysfunction agents (PDE5 inhibitors)	avanafil	↑ avanafil	Do not use PAXLOVID with avanafil because a safe and effective avanafil dosage regimen has not been established.
	sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Dosage adjustment is recommended for use of sildenafil, tadalafil, or vardenafil with PAXLOVID. Refer to individual product label for more information.
Opioid antagonists	naloxegol	↑ naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms (see section 4.3).
Sedative/hypnotics	triazolam, oral midazolam[a]	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression (see section 4.3).
Sedative/hypnotics	buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem	↑ sedative/hypnotic	A dose decrease may be needed for these drugs when co-administered with PAXLOVID and monitoring for adverse events is recommended.
	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

Table 1: Established and other potentially significant drug interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			considered, especially if more than a single dose of midazolam is administered. Refer to the midazolam product label for further information.
Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist	flibanserin	↑ flibanserin	Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression (see section 4.3).
Vasopressin receptor antagonists	tolvaptan	↑ tolvaptan	Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia (see section 4.3).

a. See section 5.2 Drug interaction studies conducted with nirmatrelvir/ritonavir.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

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

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

Pregnancy

There are limited data from the use of PAXLOVID in pregnant women. PAXLOVID should be used during pregnancy only if the potential benefits outweigh the potential risks for the mother and the fetus.

Animal data with nirmatrelvir have shown developmental toxicity in the rabbit (lower fetal body weights) but not in the rat. There was no nirmatrelvir-related effect on fetal morphology or embryo-fetal viability at any dose tested in rat or rabbit embryo-fetal developmental toxicity studies. There were no nirmatrelvir-related adverse effects in a pre- and postnatal developmental study in rats (see section 5.3).

A large number (6,100 live births) of pregnant women were exposed to ritonavir during pregnancy; of these, 2,800 live births were exposed during the first trimester. 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 PK enhancer for other protease inhibitors, similar to the ritonavir dose used for nirmatrelvir/ritonavir. These data indicate no increase in the rate of birth defects compared to rates observed in population-based birth defect surveillance systems.

Animal data with ritonavir have shown reproductive toxicity (see section 5.3).

Breast-feeding

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 breast milk 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 breast-fed 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.

Fertility

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

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile

The safety of PAXLOVID was based on data from three Phase 2/3 randomized, placebo-controlled trials in adult participants 18 years of age and older (see section 5.1):

- 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 were to present with mild-to-moderate COVID-19 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 diarrhea (2.9% and 1.9%, respectively).

Tabulated summary of adverse drug reactions (ADRs)

The adverse drug reactions in Table 2 are listed below by system organ class.

Table 2: Adverse drug reactions (ADRs) by system organ class and council for international organizations of medical sciences (CIOMS) frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

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 (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity*	Anaphylaxis*		
Nervous system disorders		Dysgeusia[a] Headache[a]				
Vascular disorders			Hypertension*			
Gastrointestinal disorders		Diarrhea[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 (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.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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 the SARS-CoV-2 M^{pro} renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication.

Ritonavir is not active against SARS-CoV-2 M^{pro}. 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.

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.

In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020.

Antiviral resistance in cell 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 3 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 3: 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), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), 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), H172Y+P252L (ND), 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).

Abbreviations: ND=no data (substitution emerged from nirmatrelvir resistance selection but has not been tested for EC_{50} determination in an antiviral assay).

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 in an antiviral cell assay. Virus containing E166V shows the greatest reduction in susceptibility to nirmatrelvir and appears to have replication defect since it either could not be generated or had a very low virus titer. 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 with hospitalization or death from the EPIC-HR or 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 hospitalization. Thus, the clinical significance of these substitutions is unknown.

Viral load rebound

Post-treatment increases in SARS-CoV-2 nasal RNA levels (i.e., viral RNA rebound) were observed on Day 10 and/or Day 14 after initiating study treatment in a subset of PAXLOVID and placebo recipients in EPIC-HR and EPIC-SR, irrespective of COVID-19 symptoms. The frequency of detection of post-treatment nasal viral RNA rebound varied according to analysis parameters but was generally similar among PAXLOVID and placebo recipients. A similar or smaller percentage of placebo recipients compared to PAXLOVID recipients had nasal viral RNA results < lower limit of quantitation (LLOQ) at all study timepoints in both the treatment and post-treatment periods.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of COVID-19-related hospitalization or death from any cause through Day 28 following the single 5-day course of PAXLOVID treatment. The clinical relevance of post-treatment increases in viral RNA following PAXLOVID or placebo treatment is unknown.

EPIC-HR and EPIC-SR were not designed to evaluate symptomatic viral RNA rebound, and most episodes of symptom rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were routinely assessed). The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among PAXLOVID and placebo recipients.

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 from baseline relative to placebo at Day 5 in viral RNA levels in nasopharyngeal samples are summarized by study in Table 4.

Table 4: Analysis of change from baseline to Day 5 in log_{10} (viral RNA levels, copies/mL); EPIC-HR and EPIC-SR (mITT1 analysis set)

	EPIC-HR (mITT1[a])		EPIC-SR (mITT1[b])	
	PAXLOVID	**Placebo**	**PAXLOVID**	**Placebo**
Primary VoC[c]	Delta (99%)		Delta (79%) Omicron (19%)	
Baseline	n=764	n=784	n=542	n=514
Median	6.075	5.990	6.615	6.430
Mean (SD)	5.780 (2.077)	5.617 (2.143)	6.214 (1.794)	6.045 (1.862)
Day 5	n=676	n=683	n=498	n=473
Median change from baseline	-2.990	-2.160	-3.680	-2.630
Median reduction relative to placebo	-0.830		-1.050	
Adjusted change from baseline, mean (95% CI)	-3.087 (-3.219, -2.955)	-2.310 (-2.439, -2.180)	-3.419 (-3.584, -3.253)	-2.551 (-2.723, -2.378)
Mean reduction relative to placebo, mean (95% CI)	-0.777 (-0.937, -0.617)		-0.868 (-1.073, -0.663)	
p-value	<0.0001		<0.0001	

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mAb=monoclonal antibody; mITT=modified intent-to-treat; RT-PCR=reverse transcriptase–polymerase chain reaction; SD=standard deviation; VoC=variant of concern.

a. All treated participants with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.
b. All treated participants with at least 1 post-baseline visit through Day 28; 57% of these participants were vaccinated against COVID-19 at baseline.
c. VoC lineage percentage relates to the entire study populations for EPIC-HR and EPIC-SR.

The degree of reduction in viral RNA levels relative to placebo following 5 days of PAXLOVID treatment was similar between unvaccinated high-risk subjects in EPIC-HR and vaccinated high-risk subjects in EPIC-SR.

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

In participants receiving placebo/ritonavir twice a day, a modest increase in cholesterol (≤27.2 mg/dL), LDL cholesterol (≤23.2 mg/dL), triglycerides (≤64.3 mg/dL) and decrease in HDL cholesterol (≤4 mg/dL) was observed. The clinical significance of such changes with short-term treatment is unknown.

Clinical efficacy

Efficacy in participants at high risk of progressing to severe COVID-19 illness (EPIC-HR)
The efficacy of PAXLOVID is based on the final analysis of EPIC-HR, a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible participants were 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. Participants with COVID-19 symptom onset of ≤5 days were included in the study.

Participants were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The study excluded individuals with a history of prior COVID-19 infection or vaccination. The primary efficacy endpoint was the proportion of participants with COVID-19 related hospitalization 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 who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment], the mITT1 analysis set (all treated participants with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated participants with onset of symptoms ≤5 days).

A total of 2,113 participants were randomized to receive either PAXLOVID or placebo. At baseline, mean age was 45 years; 51% were male; 71% were White, 4% were Black or African American, and 15% were Asian; 41% were Hispanic or Latino; 67% of participants had onset of symptoms ≤3 days before initiation of study treatment; 49% of participants were serological negative at baseline. The mean (SD) baseline viral load was 4.71 $\log_{10}$ copies/mL (2.89); 27% of participants 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 randomization and were excluded from the mITT and mITT1 analyses.

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

The proportions of participants who discontinued treatment due to an adverse event were 2.0% in the PAXLOVID group and 4.3% in the placebo group.

Table 5 provides results of the primary endpoint in the mITT1 analysis population demonstrating superiority of PAXLOVID compared to placebo for COVID-19 related hospitalization 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: 72%, 93%).

Table 5: Efficacy results in non-hospitalized 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 hospitalization 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 participants 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.

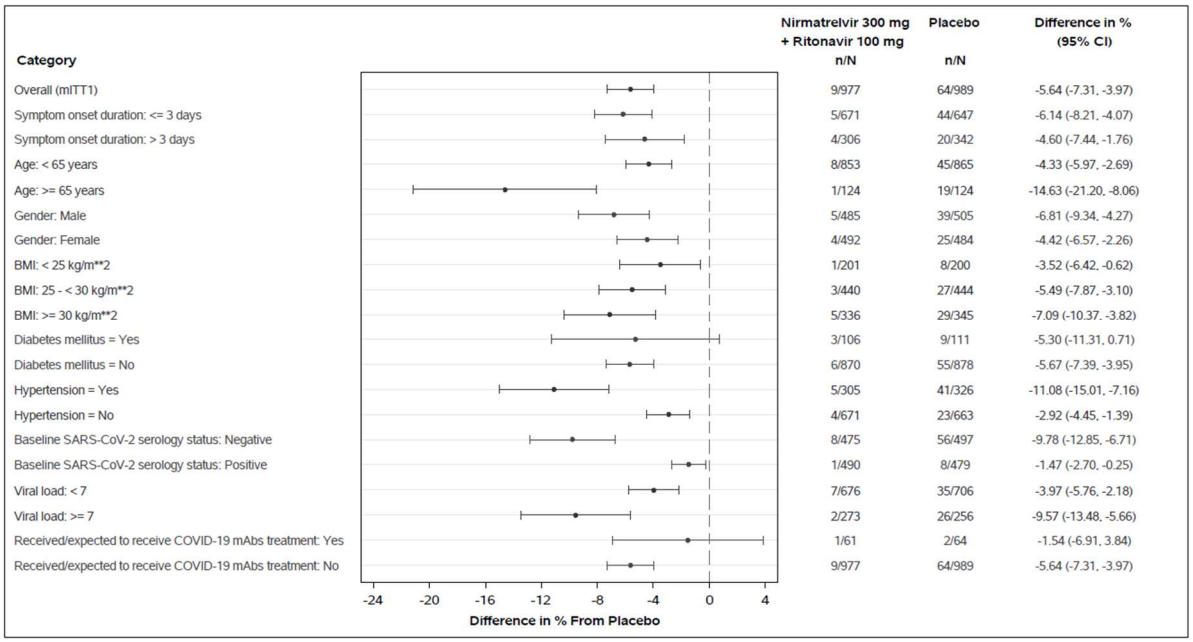
a. The estimated cumulative proportion of participants hospitalized or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where participants without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

Through Week 24, no deaths were reported in the PAXLOVID group compared with 15 deaths in the placebo group.

Consistent results were observed in the mITT and mITT2 analysis populations. A total of 1,318 participants were included in the mITT analysis population. The event rates of COVID-19 related hospitalization or death from any cause through Day 28 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).

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



Abbreviations: BMI=body mass index; 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); N=number of participants in the category of the analysis set; SARS-COV-2=severe acute respiratory syndrome coronavirus 2.
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 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, diarrhea, 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 6 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 6: 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	

Table 6: Analyses of time to sustained symptom alleviation and sustained symptom resolution through 28 days (mITT1 analysis set): EPIC-HR

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 hospitalized 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)

PAXLOVID is not indicated for the treatment of COVID-19 in patients without a risk factor for progression to severe COVID-19.

EPIC-SR was a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible participants were 18 years of age and older with COVID-19 symptom onset of ≤5 days who were at standard risk for progression to severe disease. The study included previously unvaccinated participants without risk factors or fully vaccinated participants with at least 1 of the risk factors for progression to severe disease (as defined in the EPIC-HR section above and by local regulations and practices). A total of 1,296 participants were randomized (1:1) to receive PAXLOVID or placebo orally every 12 hours for 5 days; of these, 49% were vaccinated at baseline with at least 1 risk factor for progression to severe disease.

The primary endpoint in this study, 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.

Analyses of efficacy presented below is based on an exploratory analysis of the subgroup of vaccinated participants with at least 1 risk factor for progression to severe disease. In vaccinated participants, Table 7 provides results of the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 (secondary endpoint of EPIC-SR). The relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 58%. The result did not reach statistical significance.

Table 7: Efficacy results in non-hospitalized vaccinated adults with at least 1 risk factor for progression to severe COVID-19 who were dosed within 5 days of symptom onset (mITT1 analysis set)

	PAXLOVID (N=317)	Placebo (N=314)
COVID-19 related hospitalization or death from any cause through Day 28		
n (%)	3 (0.9%)	7 (2.2%)
Reduction relative to placebo[a] (95% CI), %	-1.292 (-3.255, 0.671)	
All-cause mortality through Day 28, %	0	1 (0.3%)

Abbreviations: CI=confidence interval; COVID-19=Coronavirus Disease 2019; mITT1=modified intent-to-treat 1 (all participants randomly assigned to study intervention who took at least 1 dose of study intervention and with at least 1 post-baseline visit through Day 28).

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

Post-exposure prophylaxis (EPIC-PEP)
PAXLOVID is not indicated for the post-exposure prophylaxis of COVID-19.

EPIC-PEP was a Phase 2/3, randomized, 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 randomized (1:1:1) to receive PAXLOVID orally every 12 hours for 5 days, PAXLOVID orally every 12 hours for 10 days, or placebo.

The primary endpoint in this study, the risk reduction between the PAXLOVID 5-day and 10-day PAXLOVID regimens versus placebo in the proportion of participants who developed symptomatic reverse transcriptase–polymerase chain reaction (RT-PCR) or rapid antigen test (RAT)-confirmed SARS-CoV-2 infection through Day 14 among participants who had a negative SARS-CoV-2 RT-PCR result at baseline, was not met.

Compared with placebo, the PAXLOVID 5-day and 10-day regimens led to a 30% and 36% relative risk reduction, respectively, in the risk of developing a symptomatic, RT-PCR or RAT confirmed SARS-CoV-2 infection through household contact; these results did not reach statistical significance.

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 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 to healthy participants in the fasted state, the geometric mean (CV%) maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to the time of last measurement (AUC_{last}) was 2.88 ug/mL (25%) and 27.6 ug*hr/mL (13%), respectively. Upon repeat-dose of nirmatrelvir/ritonavir 75 mg/100 mg, 250 mg/100 mg, and 500 mg/100 mg administered twice daily, the increase in systemic exposure at steady-state appears to be less than dose proportional. Multiple dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. Systemic exposures on Day 5 were similar to Day 10 across all doses. Simulated repeat-dose exposures of nirmatrelvir/ritonavir 300 mg/100 mg administered twice daily in adult participants from EPIC-HR, suggested the mean AUC_{tau} was 28.3 µg*hr/mL, mean C_{max} was 3.29 µg/mL, and mean C_{min} was 1.40 µg/mL.

Absorption

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

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV%) C_{max} and AUC_{inf} was 0.36 µg/mL (46) and 3.60 µg*hr/mL (47), respectively. The median (range) time to C_{max} (T_{max}) was 3.98 hrs (1.48-4.20). The arithmetic mean (±SD) terminal elimination half-life was 6.1 (2.2) hours.

Effect of food on oral absorption
Dosing with a high fat meal increased the exposure of nirmatrelvir (approximately 61% increase in mean C_{max} and 20% increase in mean AUC_{last}) relative to fasting conditions following administration of 300 mg nirmatrelvir (2 × 150 mg)/100 mg ritonavir tablets.

Distribution

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

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

Biotransformation

In vitro studies assessing nirmatrelvir without concomitant ritonavir suggest that nirmatrelvir is primarily metabolized by CYP3A4. Nirmatrelvir is not a substrate of other CYP enzymes. Administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In human plasma, the only drug-related entity quantifiable was unchanged nirmatrelvir.

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

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

Elimination

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

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

Specific populations

Age and gender
In a population PK analysis, there were no clinically significant differences in the pharmacokinetics of nirmatrelvir based on age and gender.

Pediatric patients
The pharmacokinetics of nirmatrelvir/ritonavir in pediatric patients 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. In a population PK analysis, race did not affect the pharmacokinetics of nirmatrelvir.

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

Patients with hepatic impairment
Compared to healthy controls with no hepatic impairment, the pharmacokinetics of nirmatrelvir in participants with moderate hepatic impairment were not significantly different. Adjusted geometric mean ratio (90% CI) of AUC_{inf} and C_{max} of nirmatrelvir comparing moderate hepatic impairment (test) to normal hepatic function (reference) were 98.78% (70.65%, 138.12%) and 101.96% (74.20%, 140.11%), respectively.

Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Drug interaction studies conducted with nirmatrelvir

In vitro data indicates that nirmatrelvir is a substrate for human MDR1 (P-gp) and CYP3A4, but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Nirmatrelvir does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro* at clinically relevant concentrations. Nirmatrelvir has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp) and OATP1B1.

Nirmatrelvir does not induce any CYPs at clinically relevant concentrations.

Drug interaction studies conducted with nirmatrelvir/ritonavir

In vitro studies indicate that ritonavir is mainly a substrate of CYP3A. Ritonavir also appears to be a substrate of CYP2D6 which contributes to the formation of isopropylthiazole oxidation metabolite M-2.

Ritonavir is an inhibitor of CYP3A and to a lesser extent CYP2D6. Ritonavir appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including glucuronosyl transferase.

The effects of co-administration of PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarized in Table 8.

Table 8: Effect of co-administered drugs on pharmacokinetics of nirmatrelvir

Co-administered drug	Dose (schedule)		N	Percent ratio of nirmatrelvir[a] PK parameters (90% CI); no effect=100	
	Co-administered	Nirmatrelvir/ ritonavir		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 summarized in Table 9.

Table 9: 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 (4 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

Toxicology

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

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

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

Carcinogenesis

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

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

Genotoxicity

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

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

Reproductive toxicity

Nirmatrelvir
In a fertility and early embryonic development study, there were no nirmatrelvir effects on fertility and reproductive performance at doses up to 1,000 mg/kg/day representing 5× clinical exposures at the approved dose of PAXLOVID.

Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and GD 7 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC_{24}) in rats was approximately 9× higher than clinical exposures at the approved human dose of PAXLOVID. In the rabbit EFD study, lower fetal body weights (9% decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings. At 1,000 mg/kg/day, the systemic exposure (AUC_{24}) in rabbits was approximately 11× higher than clinical exposures at the approved human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed at up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC_{24}) approximately 3× higher than clinical exposures at the approved human dose of PAXLOVID.

In the pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9× higher than clinical exposures at the approved human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6× higher than clinical exposures at the approved human dose of PAXLOVID.

Ritonavir
Ritonavir produced no effects on fertility in rats.

Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 in rats and GD 6 through 19 in rabbits). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) 5× (rats) or 8× (rabbits) higher than exposure

at the approved human dose of PAXLOVID. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures approximately 10× higher than exposure at the approved human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses, at systemic exposures greater than 8× higher than exposure at the approved human dose of PAXLOVID. In a pre- and postnatal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through Postnatal Day 20 resulted in no developmental toxicity, at ritonavir systemic exposures greater than 10× the exposure at the approved human dose of PAXLOVID.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Nirmatrelvir

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

Film coating:
Hydroxy propyl methylcellulose
Iron oxide red
Polyethylene glycol
Titanium dioxide

Ritonavir

AbbVie Ritonavir (Brand name: Norvir) contains the following inactive ingredients: copovidone, dibasic calcium phosphate anhydrous / calcium hydrogen phosphate anhydrous, sorbitan monolaurate, colloidal silicon dioxide / colloidal anhydrous silica and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide E171, polyethylene glycol 400 / macrogol type 400, hydroxylpropyl cellulose, talc, polyethylene glycol 3350 / macrogol type 3350, colloidal silicon dioxide / colloidal silica anhydrous and polysorbate 80.

Refer to prescribing information of AbbVie Ritonavir (Brand name: Norvir) for the latest information.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Refer to outer carton.

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

Nirmatrelvir tablets and ritonavir tablets are supplied in separate blister cavities within the same blister card.

Each carton contains 30 tablets divided in 5 daily-dose blister cards.

Each daily blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening.

6.6. Special precautions for disposal and other handling

No special requirements for disposal.

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

7. PRODUCT OWNER

Pfizer Inc.
New York,
United States

PAX-SIN-0725/0
Date of last revision: July 2025

Package leaflet: Information for the patient

PAXLOVID film-coated tablets
nirmatrelvir + ritonavir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PAXLOVID is and what it is used for

PAXLOVID contains two active substances nirmatrelvir and ritonavir in two different tablets. PAXLOVID is an antiviral medicine used for to treat mild-to-moderate Coronavirus Disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID 19, including hospitalization or death.

COVID-19 is caused by a virus called a coronavirus. PAXLOVID stops the virus multiplying in cells and this stops the virus multiplying in the body. This can help your body to overcome the virus infection, and may prevent you from developing severe illness.

If your symptoms worsen or do not improve after 5 days, talk to your doctor.

2. What you need to know before you take PAXLOVID

Do not take PAXLOVID
- if you are allergic to nirmatrelvir, ritonavir or any of the other ingredients in PAXLOVID (listed in section 6).
- if you are taking any of the following medicines. Taking PAXLOVID with these medicines may cause serious or life-threatening side effects or affect how PAXLOVID works:
  - Alfuzosin (used to treat symptoms of an enlarged prostate)
  - Ranolazine (used to treat chronic chest pain [angina])
  - Amiodarone, dronedarone, flecainide, propafenone, quinidine (used to treat heart conditions and correct irregular heartbeats)

- Colchicine (used to treat gout)
- Lurasidone, pimozide (used to treat schizophrenia)
- Silodosin (used to treat benign prostatic hyperplasia)
- Eplerenone and ivabradine (used to treat heart and/or blood vessel problems)
- Dihydroergotamine and ergotamine (used to treat migraine headaches)
- Methylergonovine (used to stop excessive bleeding that may occur following childbirth or an abortion)
- Lovastatin, simvastatin, lomitapide (used to lower blood cholesterol)
- Voclosporin (used to treat immune disorders)
- Eletriptan, ubrogepant (used to treat migraine headaches)
- Finerenone (used to treat chronic kidney disease)
- Suzetrigine (used to treat acute pain)
- Naloxegol (used to treat opioid-induced constipation)
- Sildenafil used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery)
- Triazolam, midazolam taken orally (used to relieve anxiety and/or trouble sleeping)
- Flibanserin (used to treat hypoactive (low) sexual desire disorder (HSDD))
- Tolvaptan used to treat hyponatremia (low sodium levels in the blood)
- Apalutamide, enzalutamide (used to treat prostate cancer)
- Carbamazepine, phenobarbital, primidone, phenytoin (used to prevent and control seizures)
- Rifampin and rifapentine (used to treat bacterial infections)
- Lumacaftor/ivacaftor (used to treat cystic fibrosis)
- St. John's wort (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)

Warnings and precautions

Allergic reactions
Allergic reactions, including severe allergic reactions (known as 'anaphylaxis'), can happen in people taking PAXLOVID, even after only 1 dose. Stop taking PAXLOVID and call your doctor right away if you get any of the following symptoms of an allergic reaction:
- trouble swallowing or breathing
- swelling of the tongue, mouth, and face
- throat tightness
- hoarseness
- itching
- skin rash

Liver disease
Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-colored urine, pale colored stools and itchy skin, stomach area (abdominal) pain.

Kidney disease
Tell your doctor if you have or have had a kidney disease.

Risk of HIV-1 resistance development
If you have untreated or uncontrolled HIV infection, PAXLOVID may lead to some HIV medicines not working as well in the future.

Children and adolescents
The safety and efficacy of PAXLOVID have not been studied in patients younger than 18 years of age.

Other medicines and PAXLOVID
There are other medicines that may not be taken together with PAXLOVID. Tell your doctor(s) or pharmacist if you are taking, have recently taken or might take any other medicines:
- medicines used to treat symptoms of an enlarged prostate, such as tamsulosin
- medicines used to treat heart rhythm abnormalities (arrhythmia), such as lidocaine (systemic) and disopyramide
- medicines used to treat cancer, such as abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine and vincristine
- medicines used to thin the blood (anticoagulants), such as warfarin, rivaroxaban, dabigatran, apixaban and vorapaxar
- medicines used to treat convulsions, such as clonazepam
- medicines used to treat depression, such as bupropion and trazodone
- medicines used to treat fungal infections (antifungals), such as voriconazole, ketoconazole, isavuconazonium sulfate and itraconazole
- medicines used to treat HIV infection, such as atazanavir, darunavir, tipranavir, efavirenz, maraviroc, nevirapine, zidovudine and bictegravir/emtricitabine/tenofovir
- medicines used to treat infections (e.g., antibiotics and antimycobacterials), such as clarithromycin, erythromycin, bedaquiline and rifabutin
- medicines used to treat parasitic infections (e.g., albendazole)
- medicines used to treat schizophrenia, bipolar disorder, severe depression and abnormal thoughts or feelings, such as quetiapine, clozapine, aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone and pimavanserin
- medicines used to treat high blood pressure (hypertension), such as amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil and aliskiren
- medicines used to treat heart conditions and correct irregular heartbeats, such as digoxin
- medicines used to prevent blood clots (antiplatelets) such as ticagrelor, clopidogrel and cilostazol
- steroids including corticosteroids used to treat inflammation, such as betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone and triamcinolone
- medicines used to treat cystic fibrosis such as ivacaftor, elexacaftor/tezacaftor/ivacaftor and tezacaftor/ivacaftor
- medicines used to lower blood sugar, such as saxagliptin
- medicines used to treat high blood pressure in the blood vessels that supply the lungs, such as bosentan, tadalafil and riociguat
- medicines used to treat hepatitis C virus infection, such as elbasvir/grazoprevir, glecaprevir/pibrentasvir, ombitasvir/paritaprevir/ritonavir and dasabuvir, sofosbuvir/velpatasvir/voxilaprevir
- medicines used to lower blood cholesterol, such as atorvastatin and rosuvastatin

- medicines used to suppress your immune system, such as cyclosporine, tacrolimus, everolimus and sirolimus
- medicines used to treat autoimmune conditions, such as tofacitinib and upadacitinib
- medicines used to treat asthma and other lung-related problems such as chronic obstructive pulmonary disease [COPD], such as salmeterol
- medicines used to treat migraine headaches such as rimegepant
- medicines used to treat overactive bladder such as darifenacin
- medicines used to treat severe pain, such as fentanyl, hydrocodone, oxycodone, meperidine and methadone
- medicines used to treat erectile dysfunction (also known as impotence), such as avanafil, sildenafil, tadalafil and vardenafil
- medicines used as sedatives, hypnotics, and sleeping agent, such as buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem and suvorexant
- any of the following other specific medicines:
    - oral or patch contraceptive containing ethinyl estradiol used to prevent pregnancy
    - midazolam administered by injection (used for sedation [an awake but very relaxed state of calm or drowsiness during a medical test or procedure] or anesthesia)

Many medicines interact with PAXLOVID. **Keep a list of your medicines to show your doctor(s) and pharmacist.** Do not start taking a new medicine without telling your doctor(s). Your doctor(s) can tell you if it is safe to take PAXLOVID with other medicines.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

There is not enough information to be sure that PAXLOVID is safe for use in pregnancy. If you are pregnant, you should not take PAXLOVID unless your healthcare professional advises that you can. It is recommended that you refrain from sexual activity or use contraception while taking PAXLOVID and for 7 days after completing PAXLOVID as a precaution. If you are taking hormonal contraception, as PAXLOVID may reduce the effectiveness of this medicine, it is recommended that a condom or other non hormonal method of contraception is used. Your doctor will advise you on the duration of this required adjustment of your contraceptive measures.

A small amount of PAXLOVID passes into breast milk. You should not breast-feed your baby while taking PAXLOVID and for 48 hours after completing PAXLOVID as a precaution.

Driving and using machines
PAXLOVID has not been specifically tested for its possible effects on the ability to drive and use machines.

PAXLOVID contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take PAXLOVID

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

PAXLOVID consists of 2 medicines: nirmatrelvir and ritonavir. The recommended dose is 2 tablets of nirmatrelvir (pink tablet) with 1 tablet of ritonavir (white tablet) by mouth twice daily (in the morning and in the evening).

A course of treatment lasts 5 days. For each dose, take all 3 tablets together at the same time.

If you have kidney disease, please talk to your healthcare provider for an appropriate dose of PAXLOVID.

Swallow the tablets whole. Do not chew, break or crush the tablets. PAXLOVID can be taken with or without meals.

If you take more PAXLOVID than you should
If you take too much PAXLOVID, call your healthcare provider or go to the nearest hospital emergency room right away.

If you forget to take PAXLOVID
If you miss a dose of PAXLOVID within 8 hours of the time it is usually taken, take it as soon as you remember. If you miss a dose by more than 8 hours, skip the missed dose and take the next dose at your regular time. Do not take 2 doses of PAXLOVID at the same time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking PAXLOVID
Even if you feel better, do not stop taking PAXLOVID without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- Altered sense of taste
- Headache
- Diarrhea
- Nausea

Uncommon: may affect up to 1 in 100 people
- Allergic reactions (such as itching or skin rash)
- Increased blood pressure
- Vomiting
- Abdominal pain

Rare: may affect up to 1 in 1,000 people
- Severe allergic reaction known as 'anaphylaxis' (such as swelling of tongue, mouth and face, trouble swallowing or breathing, throat tightness, or hoarseness)
- Feeling generally unwell
- Serious skin reaction with flu-like symptoms and painful rash or blisters affecting the skin, mouth, eyes and genitals (Stevens-Johnson syndrome and toxic epidermal necrosis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store PAXLOVID

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.

Store at or below 30°C.
Do not refrigerate or freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PAXLOVID contains
- The active substances in this medicine are nirmatrelvir and ritonavir.
  - Each pink film-coated nirmatrelvir tablet contains 150 mg of nirmatrelvir.
  - Each white film-coated ritonavir tablet contains 100 mg of ritonavir.
- The other ingredients in the nirmatrelvir tablet are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate (see section 2, 'PAXLOVID contains lactose'), microcrystalline cellulose and sodium stearyl fumarate. The film-coating contains hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol and titanium dioxide.
- The other ingredients in the ritonavir tablet are copovidone, dibasic calcium phosphate anhydrous / calcium hydrogen phosphate anhydrous, sorbitan monolaurate, colloidal silicon dioxide / colloidal anhydrous silica and sodium stearyl fumarate. The film-coating contains hypromellose, titanium dioxide E171, polyethylene glycol 400 / macrogol type 400, hydroxylpropyl cellulose, talc, polyethylene glycol 3350 / macrogol type 3350, colloidal silicon dioxide / colloidal silica anhydrous and polysorbate 80. Refer to prescribing information of AbbVie Ritonavir (Brand name: Norvir) for the latest information.

What PAXLOVID looks like and contents of the pack
PAXLOVID film-coated tablets are available in 5 daily-dose blister cards with a total of 30 tablets packaged in a carton.

Each daily blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening (sun and moon symbols).

Nirmatrelvir 150 mg film-coated tablets are pink, oval-shaped and debossed with ‘PFE’ on one side and ‘3CL’ on the other side.

Ritonavir 100 mg film-coated tablets are either white, ovaloid, and debossed with [Abbott logo] and the code ‘NK’ on one side, OR white, ovaloid, and debossed with ‘NK’ on one side.

PAX-SIN-0725/PIL/0
Date of last revision: July 2025