PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# Pr**PAXLOVID™**

nirmatrelvir tablets; ritonavir tablets

Tablets, 150 mg nirmatrelvir; 100 mg ritonavir

co-packaged for oral use

Protease Inhibitor

Antiviral

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Date of Initial Authorization:
January 17, 2022

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March 20, 2025

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RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| 2 CONTRAINDICATIONS | 04/2025 |
| 7 WARNINGS AND PRECAUTIONS | 08/2023 |
| 7 WARNINGS AND PRECAUTIONS, Immune | 11/2023 |
| 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential | 08/2023 |
| 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women | 08/2024 |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

PAXLOVID (nirmatrelvir tablets; ritonavir tablets) is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

PAXLOVID is not authorized:

- For initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
- For pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- For use for longer than 5 consecutive days.

### 1.1 Pediatrics

The safety and effectiveness of PAXLOVID have not been established in pediatric patients (<18 years of age).

### 1.2 Geriatrics

Clinical studies of PAXLOVID include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy (see **14 CLINICAL TRIALS**). Of the total number of participants in the pivotal trial randomized to receive PAXLOVID (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

## 2 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions (e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).

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.

PAXLOVID is also contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir/ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance (see **Table 1** and **9 DRUG INTERACTIONS**):

**Table 1: Drugs that are contraindicated for concomitant use with PAXLOVID**

| Drug Class | Drugs Within Class that are Contraindicated with PAXLOVID | Clinical Comment |
|---|---|---|
| Alpha$_1$-Adrenoreceptor Antagonist | alfuzosin | Potential for serious reactions, such as hypotension (see **Table 4**). |
| Antianginal | ranolazine | Potential for serious and/or life-threatening reactions. |
| Antiarrhythmics | amiodarone, bepridil[a], dronedarone, flecainide, propafenone, quinidine[a] | Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias. |
| Antibiotic | fusidic acid | Potential of increased fusidic acid-associated adverse events, such as hepatitis or bone marrow suppression. |
| Anticancer | apalutamide, enzalutamide | Potential for decreased exposure of PAXLOVID and potential loss of virologic response. In addition, exposure of apalutamide may increase with co-administration of PAXLOVID that may lead to serious adverse events including seizure and fracture. |
| | neratinib | Potential for serious and/or life-threatening reactions including hepatotoxicity. |
| | venetoclax[d] | Concomitant use of strong CYP3A inhibitors, such as PAXLOVID, and venetoclax may increase the risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase. |
| Anticoagulant | rivaroxaban | Potential of increased rivaroxaban plasma concentrations which may lead to risk of increased bleeding. |
| Anticonvulsants | carbamazepine, phenobarbital, phenytoin, primidone | Decreased plasma concentration and reduced clinical effects of nirmatrelvir and ritonavir. |
| Antifungal | voriconazole | Significant reduction in voriconazole plasma concentrations and possible loss of effect (see **Table 4**). |
| Anti-gout | colchicine | Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment (see **Table 4**). |
| Antihistamines | astemizole[a], terfenadine[a] | Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias. |
| Antimycobacterial | rifampin | Decreased plasma concentration and reduced clinical effects of nirmatrelvir and ritonavir. |

| Drug Class | Drugs Within Class that are Contraindicated with PAXLOVID | Clinical Comment |
|---|---|---|
| Antipsychotics | lurasidone<br><br>pimozide | Potential for serious and/or life-threatening reactions.<br>Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias. |
| Benign Prostatic Hyperplasia Agents | silodosin | Potential for postural hypotension. |
| Cardiovascular Agents | eplerenone<br><br>ivabradine | Potential for hyperkalemia.<br><br>Potential for bradycardia or conduction disturbances. |
| Cystic fibrosis transmembrane conductance regulator potentiators | lumacaftor/ivacaftor | Potential for loss of virologic response and possible resistance. |
| Ergot Derivatives | dihydroergotamine, ergonovine, ergotamine[a], methylergonovine[a] | Potential for serious and/or life-threatening reactions, such as acute ergot toxicity characterized by vasospasm and tissue ischemia. |
| GI Motility Agent | cisapride[a] | Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias. |
| Herbal Products | St. John's wort (*Hypericum perforatum*) | May lead to loss of virologic response and possible resistance to PAXLOVID or to the class of protease inhibitors. |
| **Lipid-modifying Agents**<br><br>HMG-CoA Reductase Inhibitors<br><br>Microsomal Triglyceride Transfer Protein (MTTP) Inhibitor | <br><br>lovastatin, simvastatin<br><br>lomitapide | <br><br>Potential for serious reactions, such as risk of myopathy including rhabdomyolysis.<br><br>Potential for serious reactions, such as hepatotoxicity. |
| Long-Acting Beta-Adrenoceptor | salmeterol | May result in potential increased risk of cardiovascular adverse events associated with salmeterol. |
| Migraine Medications | eletriptan<br><br>ubrogepant | 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.<br><br>Potential for serious adverse reactions. |

| Drug Class | Drugs Within Class that are Contraindicated with PAXLOVID | Clinical Comment |
|---|---|---|
| Mineralocorticoid Receptor Antagonists | finerenone | Potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia. |
| Opioid Antagonists | naloxegol | Potential for opioid withdrawal symptoms. |
| PDE5 Inhibitors | sildenafil[b], only when used for the treatment of pulmonary arterial hypertension (PAH)<br><br>vardenafil, when used for the treatment of erectile dysfunction or PAH | Potential increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes, and prolonged erection.<br><br>Potential increase in PDE5 inhibitor associated adverse reactions including hypotension, syncope, visual changes, and prolonged erection. |
| Sedative/Hypnotics | orally administered midazolam[c], triazolam | Potential for serious and/or life-threatening reactions, such as prolonged or increased sedation or respiratory depression. |
| Serotonin Receptor 1A Agonist/Serotonin Receptor 2A Antagonist | flibanserin | Potential for hypotension, syncope, and CNS depression. |
| Vasopressin Receptor Antagonists | tolvaptan | Potential for dehydration, hypovolemia and hyperkalemia. |

a. Product no longer marketed in Canada.
b. See **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS** for co-administration of sildenafil in patients with erectile dysfunction.
c. See **Table 4** for parenterally administered midazolam. Oral formulation of midazolam is not marketed in Canada.
d. See **Table 4** for co-administration of the maintenance dose of venetoclax.

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 **9 DRUG INTERACTIONS**):

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

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

**Dosage Modification in Patients with Moderate Renal Impairment**

PAXLOVID is a combination of nirmatrelvir tablets co-packaged with ritonavir tablets. **The daily dose is two tablets of nirmatrelvir and one ritonavir tablet twice daily.** Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of 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), **reduce the dosage of PAXLOVID to one tablet of nirmatrelvir and one tablet ritonavir every 12 hours** (see **4 DOSAGE AND ADMINISTRATION**, **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**, and **10 CLINICAL PHARMACOLOGY**).

PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min).

**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. Drug-drug interactions leading to potentially serious and/or life-threatening reactions are possible due to the effects of ritonavir on the hepatic metabolism of certain drugs.

Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).

## 4 DOSAGE AND ADMINISTRATION

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir will result in plasma levels of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.

The dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. Patients should be advised to complete the full 5-day treatment course.

The 5-day treatment course of PAXLOVID should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare professional's discretion.

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

- Older age (i.e., 60 years of age and older)

- Obesity or being overweight (i.e., 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 (i.e., chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (i.e., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (i.e., genetic or metabolic syndromes and severe congenital anomalies)
- Active cancer
- Medical-related technological dependence not related to COVID-19 (i.e., tracheostomy, gastrostomy, or positive pressure ventilation)

Other medical conditions or factors (i.e., race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and is not limited to the medical conditions or factors listed above.

## 4.1 Dosing Considerations

- Concomitant Therapy with Ritonavir or Cobicistat-Containing Regimen

  No dosage adjustment is required when co-administered with other products containing ritonavir or cobicistat. Patients on ritonavir- or cobicistat-containing HIV or HCV regimen should continue their treatment as indicated.

- Drug-drug Interactions

  Consider the potential for drug interactions prior to and during PAXLOVID therapy and review concomitant medications during PAXLOVID therapy (see **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS,** and **9 DRUG INTERACTIONS**).

## 4.2 Recommended Dose and Dosage Adjustment

Recommended Dose:
The recommended dosage for PAXLOVID is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. PAXLOVID should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of symptom onset (see **10.3 Pharmacokinetics**).

Patients with Renal Impairment:
Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment (see **10.3 Pharmacokinetics, Special Populations and Conditions**). 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), reduce the dosage of PAXLOVID to **150 mg of nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet)**

**twice daily for 5 days.** Healthcare professionals should counsel patients about renal dosing instructions (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**, and **10.3 Pharmacokinetics**).

**PAXLOVID is not recommended in patients with severe renal impairment (eGFR <30 mL/min).**

Patients with 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 subjects with severe hepatic impairment (Child-Pugh Class C); therefore, PAXLOVID is not recommended for use in patients with severe hepatic impairment (see **Hepatic/Biliary/Pancreatic**).

### 4.4 Administration

PAXLOVID (both nirmatrelvir; ritonavir tablets) can be taken orally with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

### 4.5 Missed Dose

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.

## 5 OVERDOSAGE

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

| |
|---|
| For management of a suspected drug overdose, contact your regional poison control centre. |

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 2 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral<br>(co-packaged for use) | Nirmatrelvir<br>Tablet (pink): 150mg | Tablet core: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate<br>Film coat: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol and titanium dioxide |
| | Ritonavir<br>Tablet (white): 100mg | Tablet core: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate.<br>Film coat: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc and titanium dioxide. |

PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. It is supplied in two different Dose Packs and as two-dose blister cards or single-dose blister cards.

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

| Two-dose Blister Card Presentation | | |
|---|---|---|
| **Dose Packs** | **Content** | **Description** |
| **300 mg nirmatrelvir; 100 mg ritonavir** | **Each Carton Contains:**<br>30 tablets divided in 5 daily-dose blister cards | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid tablets debossed with or without the “a” logo and the code NK. |
| | **Each Blister Card[a] Contains:**<br>4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid |

| | | |
|---|---|---|
| | | tablets debossed with or without the “a” logo and the code NK. |
| **150 mg nirmatrelvir; 100 mg ritonavir** | **Each Carton Contains:**<br>20 tablets divided in 5 daily-dose blister cards | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid tablets debossed with or without the “a” logo and the code NK. |
| | **Each Blister Card[a] Contains:**<br>2 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid tablets debossed with or without the “a” logo and the code NK. |

a. Indicates which tablets need to be taken in the morning and evening.

| **Single-dose Blister Card Presentation** | | |
|---|---|---|
| **Dose Packs** | **Content** | **Description** |
| **300 mg nirmatrelvir; 100 mg ritonavir** | **Each Carton Contains:**<br>30 tablets divided in 10 blister cards | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid tablets debossed with or without the “a” logo and the code NK. |
| | **Each Blister Card Contains:**<br>2 nirmatrelvir tablets (150 mg each) and 1 ritonavir tablet (100 mg) | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid tablets debossed with or without the “a” logo and the code NK. |
| **150 mg nirmatrelvir; 100 mg ritonavir** | **Each Carton Contains:**<br>20 tablets divided in 10 blister cards | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid tablets debossed with or without the “a” logo and the code NK. |

| | | |
|---|---|---|
| | **Each Blister Card Contains:**<br>1 nirmatrelvir tablet (150 mg) and 1 ritonavir tablet (100 mg) | Nirmatrelvir tablets: Oval, pink immediate-release, film-coated tablets debossed with "PFE" on one side and "3CL" on the other side.<br><br>Ritonavir tablets: White film-coated ovaloid tablets debossed with or without the “a” logo and the code NK. |

## 7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX.**

**General**

There are limited clinical data available for PAXLOVID. Serious and unexpected adverse events may occur that have not been previously reported with PAXLOVID 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.

See **Table 1** and **Table 4** for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).

Co-administration of PAXLOVID with calcineurin inhibitors and mTOR inhibitors:

**Severe, life-threatening, and/or fatal adverse reactions due to drug interactions have been reported in patients treated with PAXLOVID.** The most commonly reported concomitant medications resulting in serious adverse reactions were calcineurin inhibitors (e.g., tacrolimus, cyclosporine).

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 **9 DRUG INTERACTIONS**).

Consider the benefit of PAXLOVID treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed (see **9 DRUG INTERACTIONS**).

**Hepatic/Biliary/Pancreatic**

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.

**Immune**

Anaphylaxis, hypersensitivity reactions (including urticaria, angioedema, dyspnea, mild skin eruptions, and pruritus), and serious skin reactions (including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS)) have been reported with PAXLOVID. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue PAXLOVID and initiate appropriate medications and/or supportive care (see **8.5 Post-Market Adverse Reactions**).

**Reproductive Health: Female and Male Potential**

Women of childbearing potential should use effective contraception during treatment with PAXLOVID. Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with PAXLOVID (see **7.1.1 Pregnant Women** and **9 DRUG INTERACTIONS**).

- **Fertility**

  There are no available human data to evaluate the effect of PAXLOVID on fertility. No effects on fertility were observed in a study performed in rats with nirmatrelvir at systemic exposures (AUC) approximately 5 times higher than clinical exposure at the authorized human dose of PAXLOVID. Ritonavir produced no effects on fertility in rats (see **Reproductive and Developmental Toxicity**).

- **Teratogenic risk**

  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) at systemic exposures (AUC) approximately 11 times higher than clinical exposure at the authorized human dose of PAXLOVID. In an embryo-fetal developmental toxicity study in pregnant rats, there was no nirmatrelvir-related effect on fetal morphology or embryo-fetal viability at systemic exposures (AUC) approximately 9 times higher than the clinical exposure at the authorized human dose of PAXLOVID. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Animal data with ritonavir have shown reproductive toxicity (see **Reproductive and Developmental Toxicity**).

**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 (see **4 DOSAGE AND ADMINISTRATION**, **2 CONTRAINDICATIONS**, and **9 DRUG INTERACTIONS**).

## 7.1 Special Populations

### 7.1.1 Pregnant Women

PAXLOVID should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus.

There are limited human data on the use of nirmatrelvir during pregnancy to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 11 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID (see **Reproductive and Developmental Toxicity**).

Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug associated risk of miscarriage. Based on prospective reports to the antiretroviral pregnancy registry of approximately 6,900 live births following exposure to ritonavir-containing regimens (including over 3,400 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.3% (95% confidence interval [CI]: 1.9% 2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4% 3.6%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

In animal reproduction studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at doses (based on body surface area conversions) or systemic exposures (AUC) greater than or equal to 3 times higher than clinical doses or exposure at the authorized human dose of PAXLOVID (see **Reproductive and Developmental Toxicity**).

### 7.1.2 Breastfeeding

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats exposed to nirmatrelvir at maternal systemic exposure (AUC) approximately 9 times higher than clinical exposures at the authorized human dose of PAXLOVID (see **Reproductive and Developmental Toxicity**). Limited published data reports that ritonavir is present in

human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition.

### 7.1.3 Pediatrics

The safety and effectiveness of PAXLOVID have not been established in pediatric patients.

### 7.1.4 Geriatrics

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy (see **14 CLINICAL TRIALS**). Of the total number of subjects in EPIC-HR randomized to receive PAXLOVID (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

## 8 ADVERSE REACTIONS

## 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

The safety of PAXLOVID is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomized, placebo-controlled trial in non hospitalized adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection (see **14 CLINICAL TRIALS**). A total of 1,038 participants received PAXLOVID and 1,053 received placebo. Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. PAXLOVID [300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir] or matching placebo were to be taken twice daily for 5 days.

Adverse events (all grades regardless of causality) in the PAXLOVID group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (5% and <1%, respectively), and diarrhea (3% and 2%, respectively). In addition, hypertension (<1%) and myalgia (<1%) occurred at a lower frequency but were reported more frequently in the PAXLOVID treatment group than the placebo treatment group.

The proportions of subjects who discontinued treatment due to an adverse event were 2% in the PAXLOVID group and 4% in the placebo group.

**Table 3. Clinical Trial Adverse Reactions**

| | PAXLOVID n = 1038 (%) | Placebo n = 1053 (%) |
|---|---|---|
| **Nervous system disorders** | | |
| Dysgeusia | 4.6 | 0.1 |
| Headache | 1.2 | 1.2 |
| **Gastrointestinal** | | |

| | | |
|---|---|---|
| Diarrhoea | 3.0 | 1.5 |
| Vomiting | 1.2 | 0.9 |

Adverse events occurring at a ≥1% frequency in the PAXLOVID group and at a greater frequency than in the placebo group.

### 8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-authorization use of PAXLOVID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Immune System Disorders: Anaphylaxis, Hypersensitivity
- Vascular Disorders: Hypertension
- Gastrointestinal Disorders: Abdominal Pain, Nausea
- General Disorders and Administration Site Conditions: Malaise
- Skin and Subcutaneous Tissue Disorders: Toxic Epidermal Necrolysis, Stevens Johnson Syndrome

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

**Serious 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.

See **Table 4** for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during PAXLOVID therapy; review concomitant medications during PAXLOVID therapy and monitor for the adverse reactions associated with the concomitant medications (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).

### 9.2 Drug Interactions Overview

**Potential for PAXLOVID to Affect Other Drugs**

PAXLOVID 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. 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 **2 CONTRAINDICATIONS**). Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in **Table 4.**

Potential for Ritonavir to Affect Other Drugs

- Ritonavir is an inhibitor of cytochrome CYP3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Drugs that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with ritonavir. Thus, co-administration of ritonavir 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. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 4.

- Ritonavir inhibits CYP2D6 and co-administration of CYP2D6 substrates with ritonavir could result in increases (up to 2-fold) in the AUC of the former, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as glucuronosyl transferase. Therefore, decreased plasma concentrations of the co-administered drugs and potential loss of therapeutic effects may signify the need for dosage alteration of these agents.

When co-administering ritonavir with any agent having a narrow therapeutic margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is warranted (see **Table 4**).

**Potential for Other Drugs to Affect PAXLOVID**

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

### 9.4 Drug-Drug Interactions

**Established or Potentially Significant Drug Interactions**

Table 4 provides listing of clinically significant drug interactions, including contraindicated drugs. The drugs listed in **Table 4** are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. **Table 5** summarizes the effects of co-administration of PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and $C_{max}$.

**Table 4 - Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interaction**

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| **Alpha1-adrenoreceptor Antagonist:** | | |
| alfuzosin | ↑ alfuzosin | Based on results of a drug interaction study with ketoconazole, another potent inhibitor of CYP3A4, a significant increase in alfuzosin exposure is |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| | | expected in the presence of ritonavir (600 mg twice daily). Therefore, alfuzosin is contraindicated with PAXLOVID (see **2 CONTRAINDICATIONS**). |
| tamsulosin | ↑ tamsulosin | Avoid concomitant use with PAXLOVID. |
| **Analgesics, Narcotic:** | | |
| fentanyl,<br>hydrocodone,<br>oxycodone,<br>meperidine,<br><br><br><br><br>tramadol<br>propoxyphene[a]<br><br><br><br><br>methadone | ↑ fentanyl<br>↑ hydrocodone<br>↑ oxycodone<br>↑ meperidine<br><br><br><br><br>↑ tramadol<br>↑ propoxyphene<br><br><br><br><br>↓ methadone | Ritonavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl, tramadol, and propoxyphene. Use tramadol and propoxyphene with caution, as dose reduction of these drugs may be needed.<br><br>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.<br><br>Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly. Dosage increase of methadone may be considered. |
| **Anesthetic:** | | |
| meperidine | ↓ meperidine<br>↑ normeperidine (metabolite) | Dosage increase and long-term use of meperidine with ritonavir are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g., seizures). |
| **Antianginal:** | | |
| ranolazine | ↑ ranolazine | Co-administration contraindicated due to potential for serious and/or life threatening reactions (see **2 CONTRAINDICATIONS**). |
| **Antiarrhythmics:** | | |
| disopyramide, lidocaine (systemic), mexiletine<br><br><br>amiodarone, bepridil[a], dronedarone, flecainide, propafenone, quinidine[a] | ↑ antiarrhythmics<br><br><br>↑ antiarrhythmics | Plasma concentrations of these drugs are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed.<br>Co-administration may lead to serious and/or life-threatening reactions, such as cardiac arrhythmias. Therefore, use of these antiarrhythmics with PAXLOVID is contraindicated (see **2 CONTRAINDICATIONS**). |
| **Antibacterial:** | | |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| fusidic acid | ↑ fusidic acid<br>↑ ritonavir | Coadministration of protease inhibitors, including ritonavir with fusidic acid is expected to increase fusidic acid, as well as the protease inhibitor concentration in plasma (see **2 CONTRAINDICATIONS**). |
| **Anticancer agents:** | | |
| apalutamide, enzalutamide | ↓ nirmatrelvir/ritonavir | Co-administration is contraindicated due to potential loss of virologic response and possible resistance (see **2 CONTRAINDICATIONS**). |
| abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, vincristine, vinblastine | ↑ anticancer agents | Serum concentrations increase when co-administered with ritonavir resulting in the potential for increased incidence of adverse events, some of which may be serious.<br>Coadministration of ritonavir with ibrutinib is not recommended due to expected increase in ibrutinib exposure that could potentially result in a risk of tumor lysis syndrome.<br>Coadministration of ritonavir with dasatinib should be avoided due to expected increase in dasatinib exposure. If the co-administration is unavoidable, close monitoring for toxicity and adasatinib dose reduction should be considered (see SPRYCEL Product Monograph).<br>Coadministration of encorafenib or ivosidenib with ritonavir should be avoided due to potential risk of serious adverse events such as QT interval prolongation. If coadministration cannot be avoided, modify encorafenib dose as recommended in the encorafenib Product Monograph.<br>Coadministration of ritonavir with nilotinib should be avoided due to expected increase in nilotinib exposure. If the co-administration is unavoidable, close monitoring for the QT interval prolongation is recommended (see TASIGNA Product Monograph).<br>Coadministration of ritonavir with abemaciclib should be avoided due to expected increase in abemaciclib exposure. If the co-administration is unavoidable, close monitoring for toxicity and abemaciclib dose reduction should be considered (see VERZENIO Product Monograph).<br>Coadministration of ritonavir with neratinib is contraindicated due to expected increase in neratinib exposure (see **2 CONTRAINDICATIONS**).<br>Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| venetoclax | ↑ venetoclax | Concomitant use of strong CYP3A inhibitors, such as ritonavir, and venetoclax may increase the risk of tumor lysis syndrome at the dose initiation and during the ramp-up phase (see **2 CONTRAINDICATIONS**).<br>For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (see VENCLEXTA Product Monograph). |
| **Anticoagulants:** | | |
| 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 Monograph for more information. |
| dabigatran[b] | ↑ dabigatran | Co-administration with PAXLOVID results in increased dabigatran exposure and an increased risk of bleeding. Depending on dabigatran indication and renal function, reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran Product Monograph for further information. |
| rivaroxaban | ↑ rivaroxaban | A study has shown that co-administration of ritonavir and rivaroxaban resulted in increased exposure of rivaroxaban which may lead to risk of increased bleeding. Co-administration of PAXLOVID and rivaroxaban is contraindicated (see **2 CONTRAINDICATIONS**). |
| warfarin | ↓ R-warfarin<br>↓ ↑ S-warfarin | Initial frequent monitoring of the INR (International Normalized Ratio) during ritonavir and warfarin co-administration is indicated. |
| **Anticonvulsants:** | | |
| clonazepam<br>ethosuximide<br>divalproex<br>lamotrigine | ↑ clonazepam<br>↑ ethosuximide<br>↓ divalproex<br>↓ lamotrigine | Plasma concentrations of clonazepam and ethosuximide are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed and clinical monitoring is recommended.<br>Plasma concentrations of divalproex and lamotrigine are expected to decrease by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose increase of these drugs may be needed. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| carbamazepine, phenobarbital, phenytoin, primidone | ↑ carbamazepine<br>↓ phenytoin<br>↓nirmatrelvir/ ritonavir | Co-administration of PAXLOVID with carbamazepine, phenobarbital, phenytoin or primidone is contraindicated (see **2 CONTRAINDICATIONS**) |
| **Antidepressants:** | | |
| amitriptyline, clomipramine, fluoxetine, imipramine, maprotiline[a], nefazodone[a], nortriptyline, paroxetine, sertraline, trimipramine, venlafaxine | ↑ antidepressants | Ritonavir dosed as a pharmacokinetic enhancer is not expected to result in any clinically meaningful increases in CYP2D6 substrates. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed. |
| bupropion | ↓ bupropion and active metabolite hydroxy bupropion | Bupropion is primarily metabolized by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir decreases bupropion levels. Monitor for an adequate clinical response to bupropion. |
| desipramine | ↑ desipramine | A study has shown that co-administration of ritonavir and desipramine resulted in increased exposure of desipramine. Dosage reduction and concentration monitoring of desipramine is recommended. |
| trazodone | ↑ trazodone | Concomitant use of ritonavir and trazodone increases concentrations of trazodone. Adverse events of nausea, dizziness, hypertension, and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor, such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered. |
| **Antiemetics:** | | |
| dronabinol[a] | ↑ dronabinol | Plasma concentrations of dronabinol are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of dronabinol may be needed. |
| **Antifungal:** | | |
| ketoconazole, isavuconazonium sulfate, itraconazole | ↑ ketoconazole<br>↑ isavuconazonium sulfate<br>↑ itraconazole<br>↑ nirmatrelvir/ritonavir | High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended. Refer to ketoconazole, isavuconazonium sulfate, and itraconazole Product Monograph for further information. |
| voriconazole | ↓ voriconazole | Co-administration of PAXLOVID with voriconazole is contraindicated (see **2 CONTRAINDICATIONS**). |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| **Antigout:** | | |
| colchicine | ↑ colchicine | For patients with renal and/or hepatic impairment:<br>• Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir. For patients with renal and/or hepatic impairment co-administration of colchicine with PAXLOVID is contraindicated (see **2 CONTRAINDICATIONS**).<br>For patients with normal renal and/or hepatic function:<br>• *Treatment of gout flares*: 0.6 mg (1 tablet) x1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.<br>• *Prophylaxis of gout flares*: If the original colchicine regimen was 0.6 mg twice daily, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.3 mg twice daily, the regimen should be adjusted to 0.3 mg once every other day.<br>• *Treatment of Familial Mediterranean fever (FMF)*: Maximum daily dose of 0.6 mg (maybe given as 0.3 mg twice a day). |
| **Anti-infective:** | | |
| clarithromycin, erythromycin | ↑ clarithromycin<br>↑ erythromycin | For patients with renal impairment, the following dosage adjustments should be considered:<br>• For patients with $CL_{CR}$ 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.<br>• For patients with $CL_{CR}$ < 30 mL/min the dose of clarithromycin should be reduced by 75%.<br>No dose adjustment for patients with normal renal function is necessary. Refer to the respective Product Monograph for anti-infective dose adjustment. |
| **Antimycobacterial:** | | |
| rifabutin | ↑ rifabutin and rifabutin metabolite<br>↓ ritonavir | Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg/day is recommended (e.g., 150 mg every other day or 3 times a week). Further dosage reduction maybe necessary. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| rifampin | ↓ ritonavir<br>↓nirmatrelvir | Co-administration of PAXLOVID with rifampin is contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered (see **2 CONTRAINDICATIONS**). |
| **Antiparasitics:** | | |
| atovaquone | ↓ atovaquone | Plasma concentrations of atovaquone are expected to decrease by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose increase of atovaquone may be needed. |
| quinine | ↑ quinine | Plasma concentrations of quinine are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of quinine may be needed. |
| **Anxiolytics/Sedative/Hypnotics:** | | |
| triazolam, midazolam, oral[a] | ↑ triazolam<br>↑ midazolam | Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Co-administration is contraindicated due to potential for extreme sedation and respiratory depression (see **2 CONTRAINDICATIONS**). |
| midazolam, parenteral[b] | ↑ midazolam | Concomitant use of parenteral midazolam with ritonavir may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. |
| buspirone, clorazepate, diazepam, estazolam[a,] flurazepam, zolpidem | ↑ Anxiolytics/Sedatives/ Hypnotics | Plasma concentrations of these drugs are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed. |
| **Benign prostatic hyperplasia agents** | | |
| silodosin | ↑ silodosin | Co-administration contraindicated due to potential for postural hypotension (see **2 CONTRAINDICATIONS**). |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| **Beta-blockers:** | | |
| metoprolol, timolol | ↑ beta-blockers | Plasma concentrations of these drugs are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed. |
| **Bronchodilator:** | | |
| theophylline | ↓ theophylline | Increased dosage of theophylline may be required; therapeutic monitoring should be considered. |
| **Calcium channel blockers:** | | |
| amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil | ↑ calcium channel blockers | Plasma concentrations of these drugs are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed. |
| **Cardiovascular agents** | | |
| eplerenone<br><br>ivabradine | ↑ eplerenone<br><br>↑ ivabradine | Co-administration with eplerenone is contraindicated due to potential for hyperkalemia (see **2 CONTRAINDICATIONS**).<br>Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances (see **2 CONTRAINDICATIONS**). |
| aliskiren,<br>ticagrelor,<br>vorapaxar<br>clopidogrel | ↑ aliskiren<br>↑ ticagrelor<br>↑ vorapaxar<br>↓ clopidogrel active metabolite | Avoid concomitant use with PAXLOVID. |
| **Corticosteroids:** | | |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| budesonide, fluticasone propionate, triamcinolone | ↑ fluticasone<br>↑ budesonide<br>↑ triamcinolone | Concomitant use of ritonavir and inhaled, injectable, or intranasal fluticasone propionate, budesonide, triamcinolone, or other glucocorticoids that are metabolized by CYP3A4 are not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid side effects, including Cushing's syndrome and adrenal suppression.<br>Concomitant use of ritonavir and fluticasone propionate, budesonide or triamcinolone can significantly increase fluticasone propionate, budesonide or triamcinolone plasma concentrations and reduce serum cortisol concentrations. Consider alternatives to fluticasone propionate, budesonide, or triamcinolone particularly for long-term use. |
| dexamethasone<br><br>prednisone | ↑dexamethasone<br>↓ ritonavir<br>↑ prednisone | Dexamethasone, which increases CYP3A activity, would be expected to increase the clearance of ritonavir resulting in decreased ritonavir plasma concentrations.<br>Plasma concentrations of dexamethasone and prednisone are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose adjustment of these drugs may be needed. |
| digoxin | ↑ digoxin | A literature report has shown that co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when co-administrating ritonavir and digoxin, with appropriate monitoring of serum levels. |
| **Cystic fibrosis transmembrane conductance regulator potentiators:** | | |
| lumacaftor/ivacaftor | ↓ nirmatrelvir/ritonavir | Co-administration contraindicated due to potential loss of virologic response and possible resistance (see **2 CONTRAINDICATIONS**). |
| ivacaftor<br><br>elexacaftor/ tezacaftor/ivacaftor<br><br>tezacaftor/ivacaftor | ↑ ivacaftor<br><br>↑ elexacaftor/ tezacaftor/ivacaftor<br><br>↑ tezacaftor/ivacaftor | Reduce dosage when co-administered with PAXLOVID. Refer to individual Product Monograph for more information. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| **Dipeptidyl peptidase 4 (DPP4) inhibitors:** | | |
| saxagliptin | ↑ saxagliptin | Dosage adjustment of saxagliptin is recommended. Refer to the saxagliptin Product Monograph for more information. |
| **Endothelin receptor antagonist:** | | |
| bosentan | ↑ bosentan | Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID.<br>Refer to the bosentan Product Monograph for further information. |
| **Ergot derivatives:** | | |
| dihydroergotamine,<br>ergotamine[a],<br>methylergonovine[a] | ↑ dihydroergotamine<br>↑ ergotamine<br>↑ 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 **2 CONTRAINDICATIONS**). |
| **Gonadotropin releasing hormone (GnRH) receptor antagonist** | | |
| elagolix | ↑ elagolix | Coadministration of elagolix with ritonavir could increase elagolix exposure due to inhibition of CYP3A and P-gp. Known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of ritonavir. Refer to the elagolix Product Monograph for dosing information with strong CYP3A4 inhibitors. |
| **HCV-Antiviral Agents** | | |
| HCV Combination Drug: | | |
| elbasvir/grazoprevir,<br>glecaprevir/pibrentasvir<br><br>ombitasvir/paritaprevir/ritonavir with or without dasabuvir[a]<br><br>sofosbuvir/velpatasvir/voxilaprevir | ↑ antiviral | Increased grazoprevir concentrations can result in ALT elevations.<br><br>Coadministration with ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure. Avoid concomitant use of glecaprevir/pibrentasvir with PAXLOVID.<br><br>Refer to the sofosbuvir/velpatasvir/voxilaprevir Product Monograph for further information.<br><br>Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or HCV drug adverse events with concomitant use. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| HCV Protease Inhibitors: | | |
| simeprevir[a] | ↑ simeprevir | A pharmacokinetic study demonstrated that concomitant administration of simeprevir 200 mg once daily with ritonavir 100 mg twice daily resulted in an increase in simeprevir concentrations. It is not recommended to co-administer PAXLOVID with simeprevir. |
| **Herbal products** | | |
| St. John's Wort (*hypericum perforatum*) | ↓ nirmatrelvir/ritonavir | Co-administration contraindicated due to potential loss of virologic response and possible resistance use (see **2 CONTRAINDICATIONS**). |
| **HIV-Antiretroviral Agents** | | |
| HIV Protease Inhibitors: | | |
| fosamprenavir | ↑ amprenavir<br>(↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | Refer to the fosamprenavir Product Monograph for details on co-administration of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily or fosamprenavir 1400 mg once daily with ritonavir 200 mg once daily. |
| atazanavir | ↑ atazanavir<br>(↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | Atazanavir plasma concentrations achieved with atazanavir 300 mg once daily and ritonavir 100 mg once daily are higher than those achieved with atazanavir 400 mg once daily.<br>Refer to the atazanavir Product Monograph fordetails on co-administration of atazanavir 300 mg once daily, with ritonavir 100 mg once daily. |
| darunavir | ↑ darunavir<br>(↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | Refer to the darunavir Product Monograph for details on co-administration of darunavir 600 mg twice daily with ritonavir 100 mg twice daily. |
| indinavir[a] | ↑ indinavir<br>(↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | Alterations in concentrations are noted when reduced doses of indinavir are co-administered with reduced dose of ritonavir.<br>The safety and efficacy of this combination have not yet been established.<br>The risk of nephrolithiasis may be increased when doses of indinavir equal to or greater than 800 mg twice daily are given with ritonavir. Adequate hydration and monitoring of the patients is warranted. |
| nelfinavir | ↑ M8 (major active metabolite of nelfinavir) | Ritonavir increases the concentrations of nelfinavir major active metabolite, M8. This interaction is likely to involve cytochrome P450 inhibition and induction. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| saquinavir | ↑ saquinavir<br>(↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | The recommended dosage regimen is saquinavir 1000 mg with ritonavir 100 mg twice daily taken within 2 hours after a meal. Dose adjustment may be needed if other HIV-protease inhibitors are used in combination with saquinavir and ritonavir.<br>Saquinavir and ritonavir should not be given together with rifampin due to risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the 3 drugs are given together.<br>In some cases, co-administration of saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis, and liver disorders, especially in patients with pre-existing liver disease. Refer to the saquinavir Product Monograph for prescribing information. |
| tipranavir | ↑ tipranavir<br>(↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | Refer to the tipranavir Product Monograph for details on co-administration of tipranavir 500 mg twice daily with ritonavir 200 mg twice daily. |
| Nucleoside Reverse Transcriptase Inhibitors: | | |
| didanosine[a] | ↓ didanosine | Dosing of didanosine and ritonavir should be separated by 2.5 hours to avoid formulation incompatibility. |
| tenofovir | ↑ tenofovir | Lopinavir/ritonavir has been shown to increase tenofovir concentrations. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovir-associated adverse events. Refer to the tenofovir Product Monograph for more information. |
| zidovudine, emtricitabine | ↓ zidovudine<br>↔ emtricitabine | For further information, refer to the respective anti-HIV drugs prescribing information. |
| Non-Nucleoside Reverse Transcriptase Inhibitors: | | |
| delavirdine[a] | ↑ ritonavir<br>↔ delavirdine | When used in combination with delavirdine, a dose reduction of ritonavir should be considered. Based on comparison to historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. The safety and efficacy of this combination (delavirdine/ ritonavir) have not been established. |
| efavirenz | ↑ efavirenz | In healthy volunteers receiving 500 mg ritonavir twice daily with efavirenz 600 mg once daily, the steady state AUC was increased by 21%. An associated increase in the AUC of ritonavir of 17% was observed. |
| nevirapine | ↑ nevirapine | For further information, refer to the respective anti-HIV drugs prescribing information. |
| Integrase Inhibitor: | | |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| raltegravir | ↓ raltegravir | A pharmacokinetic study showed that co-administration of ritonavir 100 mg twice daily and raltegravir 400 mg single dose resulted in a reduction in raltegravir plasma concentration. |
| bictegravir | ↑ bictegravir | For further information, refer to the respective anti-HIV drugs prescribing information. |
| CCR5 Antagonist: | | |
| maraviroc | ↑ maraviroc<br>(↑ AUC, ↑ $C_{max}$, ↑ $C_{min}$) | When co-administered with reduced doses of ritonavir plasma levels of maraviroc increases. The dose of maraviroc should be decreased during co-administration with ritonavir. Refer to the maraviroc Product Monograph for details on co-administration of maraviroc 150 mg twice daily with ritonavir. |
| **Hypolipidemics, HMG-CoA Reductase Inhibitors:** | | |
| lovastatin, simvastatin | ↑ lovastatin, simvastatin | The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis (see **2 CONTRAINDICATIONS**).<br>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. |
| lomitapide | ↑ lomitapide | Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold.<br>Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated (see **2 CONTRAINDICATIONS**). |
| atorvastatin, rosuvastatin[b] | ↑ atorvastatin, rosuvastatin | Caution must also be exercised, and reduced doses should be considered if ritonavir is used concurrently with atorvastatin, which is metabolized to a lesser extent by CYP3A4.<br>While rosuvastatin elimination is not dependent on CYP3A, a 2-fold increase in rosuvastatin $C_{max}$ and a 1.3-fold increase in rosuvastatin AUC was seen in a drug-drug interaction study with PAXLOVID (see **Table 6**). Atorvastatin and rosuvastatin do not need to be discontinued prior to or after completing PAXLOVID. Use the lowest doses of atorvastatin or rosuvastatin with careful monitoring for signs and symptoms of myopathy or rhabdomyolysis. If treatment with an HMG-CoA reductase inhibitor is |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| | | indicated, pravastatin or fluvastatin is recommended. |
| **Immunosuppressants:** | | |
| Calcineurin inhibitors cyclosporine, tacrolimus,<br><br>mTOR inhibitors everolimus, sirolimus | ↑ immunosuppressants<br>↑ cyclosporine<br>↑ tacrolimus<br><br>↑ everolimus<br>↑ sirolimus | Avoid concomitant use of calcineurin inhibitors or mTOR inhibitors during treatment with PAXLOVID.<br>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 Monograph and latest guidelines for further information and obtain expert consultation of a multidisciplinary group (see **7 WARNINGS AND PRECAUTIONS**). |
| **Janus kinase (JAK) inhibitors** | | |
| tofacitinib<br><br>upadacitinib | ↑ tofacitinib<br><br>↑ upadacitinib | Dosage adjustment of tofacitinib is recommended. Refer to the tofacitinib Product Monograph for more information.<br><br>Dosing recommendations for co-administration with PAXLOVID depends on the upadacitinib indication. Refer to the upadacitinib Product Monograph for more information. |
| **Kinase inhibitors (also see Anticancer agents above):** | | |
| fostamatinib | ↑ fostamatinib | Coadministration of fostamatinib with ritonavir could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia. Monitor for toxicities of fostamatinib that may require fostamatinib dose modification (see fostamatinib Product Monograph). |
| **Long-acting beta adrenoceptor agonist** | | |
| salmeterol | ↑ salmeterol | Co-administration with PAXLOVID is contraindicated (see **2 CONTRAINDICATIONS**). The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. |
| **Migraine medications:** | | |
| eletriptan | ↑ eletriptan | Co-administration of eletriptan within at least 72 hours of PAXLOVID is contraindicated due to |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| ubrogepant | ↑ ubrogepant | potential for serious adverse reactions including cardiovascular and cerebrovascular events (see **2 CONTRAINDICATIONS**).<br><br>Co-administration of ubrogepant with PAXLOVID is contraindicated due to potential for serious adverse reactions (see **2 CONTRAINDICATIONS**). |
| **Mineralocorticoid receptor antagonists:** | | |
| finerenone | ↑ finerenone | Co-administration contraindicated due to potential for serious adverse reactions including hyperkalemia, hypotension, and hyponatremia (see **2 CONTRAINDICATIONS**). |
| **Muscarinic receptor antagonists:** | | |
| darifenacin | ↑ darifenacin | The darifenacin daily dose should not exceed 7.5 mg when co-administered with PAXLOVID. Refer to the darifenacin Product Monograph for more information. |
| **Neuroleptics/Antipsychotics:** | | |
| clozapine | ↑ clozapine | If co-administration is necessary, consider reducing the clozapine dose and monitor for adverse reactions. |
| lurasidone | ↑ lurasidone | Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. Co-administration of lurasidone with PAXLOVID is contraindicated (see **2 CONTRAINDICATIONS**). |
| perphenazine, risperidone, thioridazine[a] | ↑ neuroleptics | Ritonavir dosed as a pharmacokinetic enhancer is not expected to result in any clinically meaningful increases in CYP2D6 substrates. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed. |
| pimozide | ↑ pimozide | Co-administration of PAXLOVID with pimozide is contraindicated as it may lead to serious and/or life-threatening reactions, such as cardiac arrhythmias (see **2 CONTRAINDICATIONS**). |
| quetiapine | ↑ quetiapine | Due to inhibition of CYP3A by PAXLOVID (ritonavir), co-administration of PAXLOVID with quetiapine may result in increased quetiapine concentrations. Serious and life-threatening quetiapine-related adverse reactions have been reported with CYP3A inhibitors. PAXLOVID should not be used in combination with quetiapine.<br>Monitoring and dose reduction may be required if necessary. |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| **Neuropsychiatric agents:** | | |
| suvorexant[a] | ↑ suvorexant | Avoid concomitant use of suvorexant with PAXLOVID. |
| aripiprazole, brexpiprazole, cariprazine, iloperidone[a], lumateperone[a], pimavanserin[a] | ↑ aripiprazole<br>↑ brexpiprazole<br>↑ cariprazine<br>↑ iloperidone<br>↑ lumateperone<br>↑ pimavanserin | Dosage adjustment of aripiprazole, brexpiprazole, cariprazine, iloperidone, lumateperone, and pimavanserin is recommended. Refer to individual Product Monograph or label for more information. |
| **Opioid antagonists:** | | |
| naloxegol | ↑ naloxegol | Co-administration contraindicated due to the potential for opioid withdrawal symptoms (see **2 CONTRAINDICATIONS**). |
| **Oral Contraceptive or Patch Contraceptive:** | | |
| ethinyl estradiol | ↓ ethinyl estradiol | Co-administration with ritonavir results in reduced ethinyl estradiol concentrations. Dosage increase or alternate contraceptive measures should be considered. An additional, non-hormonal method of contraception should be considered during the 5 days of PAXLOVID treatment and until one menstrual cycle after stopping PAXLOVID. |
| **PDE5 Inhibitors (erectile dysfunction agents):** | | |
| sildenafil, tadalafil, vardenafil | ↑ sildenafil | Particular caution should be used when prescribing PDE5 inhibitors for the treatment oferectile dysfunction in patients receiving PAXLOVID. Co-administration of PAXLOVID with these drugs is expected to substantially increase their concentrations and may result in increase in associated adverse events, such as hypotension, syncope, visual changes, and prolonged erection.<br>Use of PDE5 Inhibitors for Erectile Dysfunction<br>Sildenafil may be used with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.<br>Tadalafil may be used with caution at reduceddoses of 10 mg every 72 hours with increased monitoring for adverse events.<br>Vardenafil should not be used with PAXLOVID (see **2 CONTRAINDICATIONS**). |
| **PDE5 Inhibitors (pulmonary hypertension agents):** | | |

| Concomitant Drug Class: Drug Name | Effect on Concentration of PAXLOVID or Concomitant Drug | Clinical Comment |
|---|---|---|
| sildenafil (Revatio®) | ↑ sildenafil | Co-administration of sildenafil with PAXLOVID is contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope (see **2 CONTRAINDICATIONS**). |
| tadalafil (Adcirca®) | ↑ tadalafil | Avoid concomitant use of tadalafil with PAXLOVID. |
| **sGC stimulators (pulmonary hypertension agents):** | | |
| riociguat | ↑ riociguat | Dosage adjustment is recommended for riociguat. Refer to the riociguat Product Monograph for more information. |
| **Serotonin receptor 1A agonist/ serotonin receptor 2A antagonist:** | | |
| flibanserin | ↑ flibanserin | Co-administration contraindicated due to potential for hypotension, syncope, and CNS depression (see **2 CONTRAINDICATIONS**). |
| **Stimulants:** | | |
| Methamphetamine | ↑ methamphetamine | Ritonavir dosed as a pharmacokinetic enhancer is not expected to result in any clinically meaningful increases in CYP2D6 substrates. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed. |
| **Vasopressin receptor antagonists:** | | |
| tolvaptan | ↑ tolvaptan | Co-administration contraindicated due to potential for dehydration, hypovolemia and hyperkalemia (see **2 CONTRAINDICATIONS**). |

a. Product not marketed in Canada.

b. See **Table 6** and **10.3 Drug Interaction Studies Conducted with Nirmatrelvir**.

↑ Indicates increase; ↓ indicates decrease; ↔ indicates no change.

**Table 5: Drug Interactions: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the Co-administered Drugs**

| Co-administered Drug | Dose (Schedule) | | | Percent Ratio of Nirmatrelvir[a] PK Parameters (90% CI); No Effect=100 | |
|---|---|---|---|---|---|
| | Co-administered Drug | Nirmatrelvir/ ritonavir | N | $C_{max}$ | AUC[b] |
| carbamazepine[c] | 300 mg twice daily (16 doses) | 300 mg/100 mg once daily (2 doses) | 10 | 56.82 (47.04, 68.62) | 44.50 (33.77, 58.65) |
| itraconazole | 200 mg once daily (8 doses) | 300 mg/100 mg twice daily (5 doses) | 11 | 118.57 (112.50, 124.97) | 138.82 (129.25, 149.11) |

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

a. Percent ratio of test (i.e., carbamazepine or itraconazole in combination with nirmatrelvir/ritonavir)/reference (i.e., nirmatrelvir/ritonavir alone).
b. For carbamazepine, AUC=$AUC_{inf}$, for itraconazole, AUC=$AUC_{tau}$.
c. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

The effects of co-administration of PAXLOVID with midazolam (CYP3A4 substrate), dabigatran (P-gp substrate), or rosuvastatin (OATP1B1 substrate) on the midazolam, dabigatran, and rosuvastatin $AUC_{inf}$ and $C_{max}$, respectively, are summarized in **Table 6.**

**Table 6: 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.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 3C-like protease main protease (Mpro), also referred to as 3CLpro or NSP5 protease. Inhibition of the SARS-CoV-2 3CL protease renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS CoV-2 3CL protease in a biochemical assay with a Ki value of 3.1 nM and an $IC_{50}$ value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 3CL protease active site by X-ray crystallography.

Ritonavir is an HIV-1 protease inhibitor but is not active against the SARS-CoV-2 3CL protease. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

## 10.2 Pharmacodynamics

Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.

## 10.3 Pharmacokinetics

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

Ritonavir is administered with nirmatrelvir as a pk (pharmacokinetic) 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. The pharmacokinetic properties of nirmatrelvir; ritonavir are displayed in Table 7.

**Table 7: Pharmacokinetic Properties of Nirmatrelvir and Ritonavir in Healthy Subjects**

| | Nirmatrelvir (When Given with Ritonavir) | Ritonavir |
|---|---|---|
| **Absorption** | | |
| $T_{max}$ (h), median | 3.00[a] | 3.98[a] |
| Food effect | Test/Reference (fed/fasted) ratios of geometric means (90% Confidence Interval) $AUC_{last}$ and $C_{max}$ for nirmatrelvir were 120.9 (109.3 – 133.7) and 161.0 (139.1 – 186.4), respectively[b] | |
| **Distribution** | | |
| % bound to human plasma proteins | 69% | 98-99% |
| Blood-to-plasma ratio | 0.60 | 0.14[d] |
| $V_z/F$ (L), mean | 104.7 [c] | 112.4 [c] |
| **Elimination** | | |
| Major route of elimination | Renal elimination[e] | Hepatic metabolism |
| Half-life ($t_{1/2}$) (hr), mean | 6.05[a] | 6.15[a] |
| Oral clearance (CL/F), mean | 8.99[c] | 13.92[c] |
| **Metabolism** | | |
| Metabolic pathways | Minimal[e] | Major CYP3A4, Minor CYP2D6 |
| **Excretion** | | |
| % drug-related material in feces | 35.3%[f] | 86.4%[g] |
| % drug-related material in urine | 49.6%[f] | 11.3%[g] |

a. Represents data after a single dose of 300 mg nirmatrelvir (2 x 150 mg tablet formulation) administered together with 100 mg ritonavir tablet in healthy subjects.
b. Following a single oral dose of nirmatrelvir 300 mg boosted with ritonavir 100 mg at -12 hours, 0 hours, and 12 hours, administered under fed (high fat, high calorie meal) (Test) or fasted (Reference) conditions.
c. 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
d. Red blood cell to plasma ratio.
e. Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.
f. Determined by $^{19}$F-NMR analysis following 300 mg oral suspension enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours, and 24 hours.
g. Determined by $^{14}$C analysis following 600 mg $^{14}$C-ritonavir oral solution.

The Single dose pharmacokinetic data of PAXLOVID in healthy subjects is depicted below in Table 8.

**Table 8: Single Dose Pharmacokinetics of Nirmatrelvir Following Dosing with 300 mg/100 mg Nirmatrelvir/Ritonavir in Healthy Subjects**

| PK Parameter (units) | Nirmatrelvir (N=12) |
|---|---|
| $C_{max}$ (µg/mL) | 2.21 (33) |
| $AUC_{inf}$ (µg*hr/mL) | 23.01 (23) |
| $T_{max}$ (hr) | 3.00 (1.02-6.00) |
| $T_{1/2}$ (hr) | 6.05 ± 1.79 |

Represents data from 2 x 150 mg tablets of nirmatrelvir. Values are presented as geometric mean (geometric % CV) except median (range) for Tmax and arithmetic mean ± SD for T1/2.

**Absorption**

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean nirmatrelvir (CV%) $C_{max}$ and area under the plasma concentration-time curve from 0 to infinity ($AUC_{inf}$) was 2.21 µg/mL (33) and 23.01 µg*hr/mL (23), respectively. The median (range) time to $C_{max}$ ($T_{max}$) was 3.00 hrs (1.02-6.00). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (1.8) hours. Following oral administration of nirmatrelvir /ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV%) $C_{max}$ and $AUC_{inf}$ was 0.36 µg/mL (46) and 3.60 µg*hr/mL (47), respectively. The median (range) time to $C_{max}$ ($T_{max}$) was 3.98 hrs (1.48-4.20). The arithmetic mean (+SD) terminal elimination half-life was 6.1 (2.2) hours.

Effect of food on oral absorption:

In healthy subjects, administration of a single oral dose of nirmatrelvir 300 mg (2 x 150 mg tablets) boosted with ritonavir 100 mg (1 x 100 mg tablet) at -12 hours, 0 hours, and 12 hours, under fed conditions (high fat and high calorie meal) increased the exposure of nirmatrelvir relative to fasting conditions. There was an approximate 61% increase in nirmatrelvir mean $C_{max}$ and a 21% increase in nirmatrelvir mean $AUC_{last}$ relative to fasting conditions. There was a delay in the median $T_{max}$ by 0.21 hours when dosed with the high fat, high calorie meal compared to fasting conditions. PAXLOVID can be taken orally with or without food.

**Distribution**

The protein binding of nirmatrelvir in human plasma is approximately 69%. The protein binding of ritonavir in human plasma is approximately 98-99%.

**Metabolism**

In vitro studies assessing nirmatrelvir without concomitant ritonavir suggest that nirmatrelvir is primarily metabolized by CYP3A4. Nirmatrelvir is not an inducer or substrate of other CYP enzymes. Administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In plasma, the only drug-related entity observed was unchanged nirmatrelvir. Minor oxidative metabolites were observed in the feces and urine.

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

Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other products metabolized by CYP3A4) and other protease HIV 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. In plasma, the only drug related entity quantifiable was unchanged nirmatrelvir.

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

**Special Populations and Conditions**

- **Age/Gender/Race** In a population PK analysis, age, gender and race did not affect the pharmacokinetics of nirmatrelvir.
- **Pediatrics** The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been evaluated.
- **Hepatic Insufficiency** A single oral dose of 100 mg nirmatrelvir administered at 0 hours enhanced with 100 mg ritonavir administered at -12 hours, 0 hours, 12 hours and 24 hours in subjects with moderate hepatic impairment resulted in similar nirmatrelvir exposures compared to subjects with normal hepatic function (see **Table 9**). 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. Ritonavir mean $C_{max}$ and $AUC_{12}$ were increased by 84% and 68%, respectively, after the second dose in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. Nirmatrelvir/ritonavir has not been studied in subjects with severe hepatic impairment.

**Table 9: Impact of Hepatic Impairment on Nirmatrelvir Pharmacokinetics**

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

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

- **Renal Insufficiency** An open-label study compared nirmatrelvir/ritonavir pharmacokinetics in healthy adult subjects and subjects with mild (eGFR 60 - <90 mL/min), moderate (eGFR ≥30 to <90 mL/min), and severe (eGFR <30 mL/min) renal impairment following administration of a single oral dose of nirmatrelvir 100 mg enhanced with ritonavir 100 mg administered at -12, 0, 12, and 24 hours. Compared to healthy controls with no renal impairment, the $C_{max}$ and AUC of nirmatrelvir in patients with mild renal impairment was 30% and 24% higher, in patients with moderate renal impairment was 38% and 87% higher, and in patients with severe renal impairment was 48% and 204% higher, respectively.

**Table 10: Impact of Renal Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics**

| | Normal Renal Function (n=8) | Mild Renal Impairment (n=8) | Moderate Renal Impairment (n=8) | Severe Renal Impairment (n=8) |
|---|---|---|---|---|

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

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

## 11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C).

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

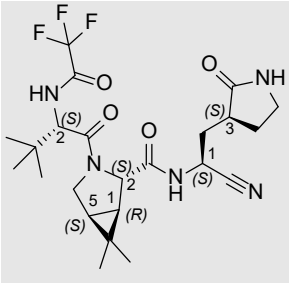
### Drug Substance

Proper name: nirmatrelvir

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

Molecular formula and molecular mass: $C_{23}H_{32}F_3N_5O_4$ and a molecular weight of 499.54.

Structural formula:



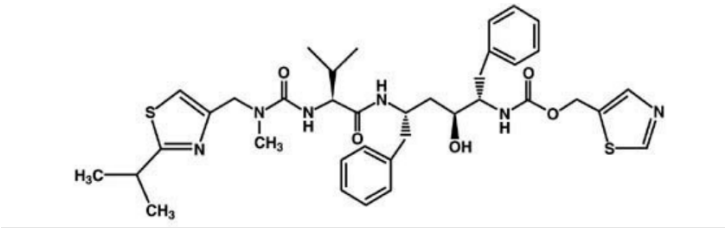
Physicochemical properties: nirmatrelvir is a white to pale coloured powder with a melting onset of approximately 192 °C. Nirmatrelvir is soluble in 1-Butanol, Methyl isobutyl ketone (MIBK), and Isopropyl acetate. It is sparingly soluble in n-Propyl acetate, n-Butyl acetate, and Anisole, and very slightly soluble in n-Heptane and water.

Proper name: ritonavir

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

Molecular formula and molecular mass: $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95.

Structural formula:



Physicochemical properties: ritonavir is a white to light tan powder and has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

Treatment of Non-Hospitalized, High-Risk Patients with Mild-to-Moderate COVID-19.

Efficacy in Participants at High Risk of Progressing to Severe COVID-19 Illness

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. The analysis was conducted in the modified intent-to-treat (mITT) analysis set [all treated participants with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb(monoclonal antibody) 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.

Table 11 provides results of the primary endpoint in the mITT1 analysis population. For the primary endpoint, the relative risk reduction in the mITT1 analysis population for PAXLOVID compared to placebo was 86% (95% CI: 72%, 93%).

**Table 11: Efficacy results in non-hospitalized adults with COVID-19 dosed within 5 days of symptom onset who did not receive COVID-19 mAb (monoclonal antibody) 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=A 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 (monoclonal antibody) 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.

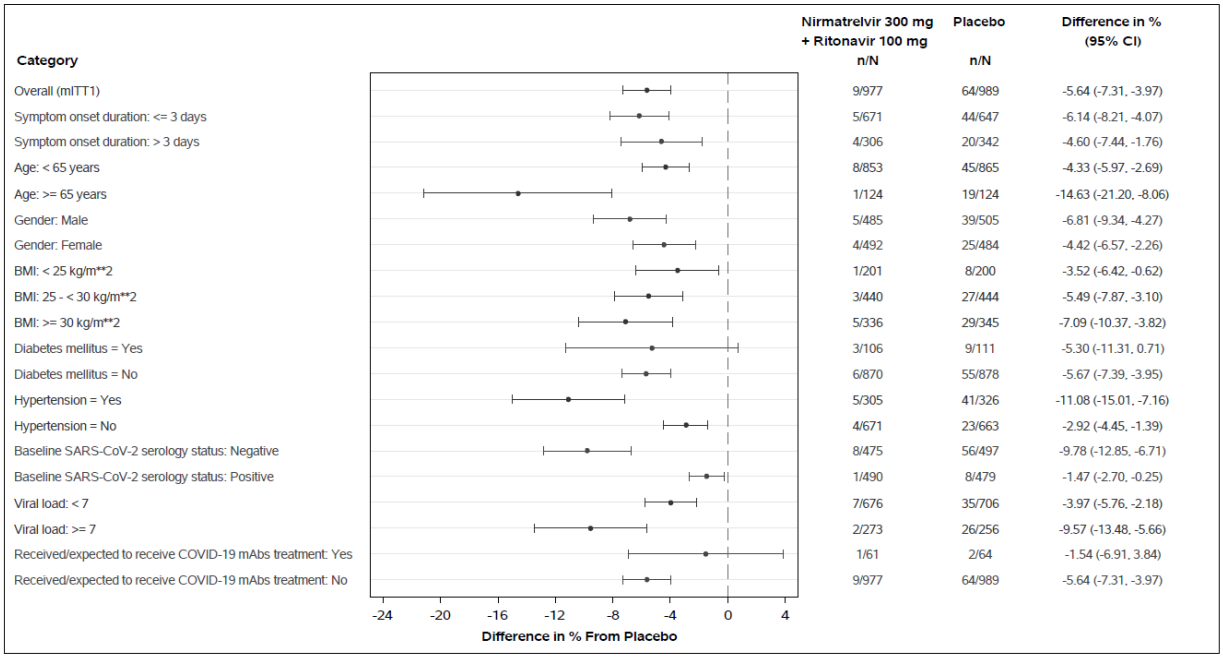
a. The estimated cumulative proportion of participants related to hospitalization or death by Day 28 was calculated for each treatment group using the Kaplan-Meier method, where participants without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

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

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 were 5/671 (0.75%) in the PAXLOVID group, and 44/647 (6.80%) in the placebo group. The primary SARSCoV2 variant across both treatment arms was Delta (98.5%), including clades 21J, 21A, and 21I.

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=A 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 (monoclonal antibody) 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.

## 15 MICROBIOLOGY

Antiviral Activity

*In vitro antiviral activity*:

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) 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

Resistance *in vitro (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 12 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 12: SARS-CoV-2 $M^{pro}$ amino acid substitutions selected by nirmatrelvir in cell culture**

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

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 from the EPIC-HR study.

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.

Resistance *in vivo and treatment-emergent substitutions*

Among subjects in clinical trial EPIC-HR with sequence analysis data available at both baseline and a post-dose sample, the following SARS-CoV-2 $M^{pro}$ or $M^{pro}$ cleavage site amino acid changes were detected as treatment-emergent substitutions that were more common in nirmatrelvir/ritonavir-treated subjects relative to placebo-treated subjects; Mpro substitutions: A7S/T/V, L30F, M49I/R/del, M82I/R, P132L/S, C145F/R/Y, E166V, T190I, T196A/K/M/R, A260D/T/V, A266P/V, V297A/F/del, T4249/R/del, A4254S/del, and L6451F/H/I; Mpro ORF1ab cleavage site substitutions: A5328P/S, and T6449I/P.

None of these substitutions in $M^{pro}$ or cleavage sites occurred in PAXLOVID-treated participants who also experienced hospitalization. Thus, the clinical significance of these substitutions is unknown.

Treatment-emergent substitutions were evaluated among participants in clinical trials EPIC-HR with sequence data available at both baseline and a post-baseline visit. 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 in a subset of PAXLOVID and placebo recipients in EPIC-HR, 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.

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 was not designed to evaluate symptomatic viral RNA rebound; the frequency of combined viral RNA rebound plus symptom rebound could not be fully assessed as most episodes of symptom

rebound occurred after Day 14 (the last day SARS-CoV-2 RNA levels were assessed). The frequency of symptom rebound through Day 28, irrespective of viral RNA results, was similar among PAXLOVID and placebo recipients.

Post-treatment nasal viral RNA rebounds were not clearly associated with drug resistance as measured using $M^{pro}$ sequencing of SARS-CoV-2 nasal viral RNA. Thus, the clinical relevance of the emergent EPIC-HR $M^{pro}$ gene substitutions remains unclear.

*Cross-resistance*

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

## 16 NON-CLINICAL TOXICOLOGY

No non-clinical studies have been conducted with nirmatrelvir in combination with ritonavir.

**General Toxicology:**

Nirmatrelvir:

Studies with nirmatrelvir included 1-month repeat-dose toxicity studies in rats and monkeys. Repeated daily oral dosing in rats at up to 1000 mg/kg/day resulted in non-adverse hematological, liver, and thyroid effects. All of the hematology and coagulation findings (prolongations in prothrombin time and activated partial thromboplastin time) had no clinical or microscopic correlates and all findings completely recovered at the end of the 2-week recovery period. The liver (minimal to mild periportal hepatocyte hypertrophy and vacuolation), thyroid gland (thyroid follicular cell hypertrophy), and pituitary gland (vacuolation in the endocrine cells of the pars anterior) findings were consistent with secondary adaptive effects related to microsomal enzyme-induced increase in thyroid hormone clearance in the liver, a mechanism that rats are known to be particularly sensitive to relative to humans. These findings were low severity and occurred in the absence of correlating alterations in clinical pathology parameters. No adverse effects were observed at 1000 mg/kg/day, which correspond to an exposure approximately 8 times higher than clinical exposures at the maximum recommended human dose of PAXLOVID. Nirmatrelvir-related findings following repeat oral dosing in monkeys at up to 600 mg/kg/day were limited to emesis, increase in fibrinogen, as well as increases in ALT and AST levels. These findings completely recovered at the end of the 2-week recovery period. Increased fibrinogen may be attributed to an inflammatory state but lacked a microscopic correlate. At the high dose of 600 mg/kg/day, the systemic exposure in monkeys was about 14 times higher than exposures at the maximum recommended human dose of PAXLOVID.

Ritonavir:

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

**Carcinogenicity:**

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

Nirmatrelvir:

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

Ritonavir:

Carcinogenicity studies in mice and rats have been conducted on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 2 times higher (in males) than the exposure in humans at the maximum recommended human dose of PAXLOVID. There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 4 times higher (in females) than the exposure in humans at the maximum recommended human dose of PAXLOVID. In rats dosed at levels of 7, 15, or 30 mg/kg/day, there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 36% that of the exposure in humans at the maximum recommended human dose of PAXLOVID.

**Genotoxicity:**

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

Nirmatrelvir:

Nirmatrelvir was not genotoxic in a battery of assays, including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells, and *in vivo* rat micronucleus assays.

Ritonavir:

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 and Developmental Toxicology:**

Nirmatrelvir:

In a fertility and early embryonic development study conducted in rats, there were no Nirmatrelvir-related effects on fertility and reproductive performance at doses up to 1000 mg/kg/day, representing systemic exposure ($AUC_{24}$) approximatively 5 times higher than clinical exposures at the maximum recommended human 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 times higher than clinical exposures at the maximum recommended 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 times higher than clinical exposures at the maximum recommended human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure ($AUC_{24}$) approximately 3 times higher than clinical exposures at the maximum recommended human dose of PAXLOVID.

In a pre- and postnatal developmental (PPND) study in pregnant rats, nirmatrelvir was administered orally at doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease (8% in males and females) in the body weight of offspring was observed at postnatal day (PND) 17. No significant differences in offspring body weight were observed after PND 28. The maternal systemic exposure ($AUC_{24}$) at 1,000 mg/kg/day was approximately 9 times higher than clinical exposures at the maximum recommended human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, resulting in systemic exposure ($AUC_{24}$) approximately 6 times higher than clinical exposures at the maximum recommended 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) approximately 4 times higher than exposure at the maximum recommended 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 4 times higher than exposure at the maximum recommended human dose of PAXLOVID. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the maximum recommended human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses approximately 11 times higher than the maximum recommended human dose of PAXLOVID, based on a body surface area conversion factor.

In pre- and post-natal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through post-natal day 20 resulted in no developmental toxicity, at ritonavir doses 3 times higher than the maximum recommended human dose of PAXLOVID, based on a body surface area conversion factor.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

**PrPAXLOVID™**

**Nirmatrelvir Tablets and Ritonavir Tablets**

Read this carefully before you start taking **PAXLOVID**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PAXLOVID**.

**Serious Warnings and Precautions**

**Patients with kidney problems**: Tell your healthcare professional before you take PAXLOVID if you have any kidney problems. You might need a lower dose of PAXLOVID. Your healthcare professional will prescribe a dose that is right for you.

**Serious interactions with other medicines**: Many medicines interact with PAXLOVID. Taking PAXLOVID with these medicines may cause serious or life-threatening side effects. Tell your healthcare professional about all the medicines you take before you start taking PAXLOVID. Do not take PAXLOVID if you are taking any of the medicines listed under the "Do not use PAXLOVID if:" section, below. Talk to your healthcare professional first before taking any new medicines. They will tell you if it is safe to take.

**What is PAXLOVID used for?**
PAXLOVID is used in adults to treat mild to moderate coronavirus disease 2019 (COVID-19) in patients who:

- have a positive result from a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral test and
- who have a high risk of getting severe COVID-19, including hospitalization or death.

PAXLOVID IS NOT approved for any of the following:

- To treat patients who are hospitalized due to severe or critical COVID-19.
- To prevent COVID-19.
- To be used for longer than 5 days in a row.
- For use in children and adolescents less than 18 years of age.

**How does PAXLOVID work?**
COVID-19 is caused by a virus called a coronavirus. PAXLOVID contains two antiviral medicines co-packaged together, nirmatrelvir and ritonavir. PAXLOVID stops the virus from multiplying. This can help your body to overcome the virus infection and may help you get better faster.

**What are the ingredients in PAXLOVID?**

**Nirmatrelvir**
Medicinal ingredients: nirmatrelvir.

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The film-coating contains hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol and titanium dioxide.

**Ritonavir**
Medicinal ingredients: ritonavir.

Non-medicinal ingredients in ritonavir: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The film-coating contains colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol, polysorbate 80, talc and titanium dioxide.

**PAXLOVID comes in the following dosage forms:**

PAXLOVID consists of two medicines co-packaged together:
- Nirmatrelvir (pink tablet): 150 mg in each tablet
- Ritonavir (white tablet): 100 mg in each tablet

Paxlovid is supplied in two different Dose Packs and as two-dose blister cards or single-dose blister cards. The Dose Packs differ in the number of blisters and nirmatrelvir tablets they contain. Your healthcare professional will prescribe the Dose Pack that is right for you.

Each Dose Pack contains the following:

| **Two-dose Blister Cards** | | |
|---|---|---|
| **Dose Packs** | **Each Carton Contains** | **Each Daily Blister Card Contains** |
| 300 mg nirmatrelvir (as two 150 mg tablets); 100 mg ritonavir | 30 tablets divided in 5 daily-dose blister cards | 4 pink nirmatrelvir tablets (150 mg each) and<br><br>2 white ritonavir tablets (100 mg each) |
| 150 mg nirmatrelvir; 100 mg ritonavir | 20 tablets divided in 5 daily-dose blister cards | 2 pink nirmatrelvir tablets (150 mg each) and<br><br>2 white ritonavir tablets (100 mg each) |
| **Single-dose Blister Cards** | | |
| **Dose Packs** | **Each Carton Contains** | **Each Blister Card Contains** |
| 300 mg nirmatrelvir (as two 150 mg tablets); 100 mg ritonavir | 30 tablets divided in 10 single-dose blister cards | 2 pink nirmatrelvir tablets (150 mg each) and<br><br>1 white ritonavir tablet (100 mg) |
| 150 mg nirmatrelvir; 100 mg ritonavir | 20 tablets divided in 10 single-dose blister cards | 1 pink nirmatrelvir tablet (150 mg) and<br><br>1 white ritonavir tablet (100 mg) |

**Do not use PAXLOVID if:**
- You are allergic to nirmatrelvir, ritonavir or to any of the other ingredients in PAXLOVID (see What are the ingredients in PAXLOVID?).
- **You are taking any of the following medicines:**
  - alfuzosin, used to treat signs and symptoms of an enlarged prostate gland

- amiodarone, bepridil*, dronedarone, flecainide, propafenone, quinidine*, used to treat irregular heartbeats
- apalutamide, enzalutamide, used for prostate cancer
- astemizole* or terfenadine*, used to relieve allergy symptoms
- carbamazepine, phenobarbital, primidone, phenytoin, typically used to treat seizures (epilepsy)
- cisapride*, used to relieve certain stomach problems
- colchicine, when used in patients with kidney and/or liver problems, used to treat gout
- eletriptan, ubrogepant, used to treat migraine
- eplerenone, ivabradine, used to treat heart failure and high blood pressure
- ergotamine*, dihydroergotamine (used to treat headaches), ergonovine, methylergonovine* (used after labour and delivery or abortion)
- finerenone, used to treat adults with chronic kidney disease and type 2 diabetes
- flibanserin, used to treat hypoactive sexual desire disorder in women
- fusidic acid, used as an antibiotic
- lovastatin, lomitapide or simvastatin, used to lower cholesterol
- lumacaftor/ivacaftor, used to treat cystic fibrosis
- lurasidone, pimozide, used to treat mental health problems
- naloxegol, used to treat constipation caused by narcotic pain medications
- neratinib, used to treat breast cancer
- ranolazine, used to treat chronic angina (chest pain)
- rifampin (used to treat tuberculosis) together with saquinavir/ritonavir (anti-HIV medication)
- rivaroxaban, used as an anticoagulant
- salmeterol, used for asthma and chronic obstructive pulmonary disease
- sildenafil, when used for the treatment of pulmonary arterial hypertension (PAH)
- silodosin, used to treat signs and symptoms of an enlarged prostate gland
- St. John's Wort (*Hypericum perforatum*), an herbal product used to treat depression
- tolvaptan, used to treat low sodium in the blood
- triazolam and midazolam (oral* or injected), used to relieve anxiety and/or trouble sleeping
- PDE5 inhibitors vardenafil, used to treat erectile dysfunction
- venetoclax, used to treat chronic lymphocytic leukemia
- voriconazole, used as an antifungal

* Product is not or no longer marketed in Canada

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PAXLOVID. Talk about any health conditions or problems you may have, including if you:**

- Have kidney problems
- Have liver problems including hepatitis
- Have human immunodeficiency virus (HIV) infection

**Other warnings you should know about:**

**Liver problems:** Before you take PAXLOVID tell your healthcare professional if you have any liver problems. Liver problems have happened in patients taking ritonavir, a medicine in PAXLOVID. Talk to your healthcare professional if you get any symptoms of liver problems. These include: yellow skin or

whites of eyes, nausea, tiredness or feeling unwell, loss of appetite, fever, skin rash, abdominal pain, pale stool or dark coloured urine.

**Pregnancy and Birth Control:** Tell your healthcare professional if you are pregnant, think you might be pregnant or are planning to become pregnant. You should not take PAXLOVID if you are pregnant unless your healthcare professional advises that you can. Women should use effective birth control while they are taking PAXLOVID. PAXLOVID may reduce the effectiveness of birth control pills, patches and vaginal rings. You should use an additional non-hormonal birth control method such as a condom, or spermicide while you are taking PAXLOVID. Continue to use the additional contraception method until your next period. Talk to your healthcare professional about effective methods of birth control.

**Breastfeeding**: Tell your healthcare professional if you are breastfeeding or plan to breastfeed. PAXLOVID can pass into your breastmilk. Your healthcare professional will tell you if you can breastfeed your baby while taking PAXLOVID.

**Severe Allergic Reactions and Severe Skin Reactions:** Before you take PAXLOVID tell your healthcare professional if you are allergic to nirmatrelvir, ritonavir or to any other ingredient in PAXLOVID. You must not use PAXLOVID if you are allergic to any of its ingredients. Allergic reactions have happened in patients taking PAXLOVID, even after only one dose. These include skin rash, hives, itching of the skin, swelling under the skin, swelling of the mouth, lips, tongue, face, and extremities, swelling and tightness of the throat, hoarseness, low blood pressure, fainting, weakness, difficulty in swallowing or breathing. If you experience signs of a severe allergic reaction and / or severe skin reactions, you should immediately stop taking PAXLOVID and consult your healthcare professional.

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have happened in patients taking ritonavir, a medicine in PAXLOVID. These are severe skin rashes / reactions. The signs of Stevens Johnson syndrome (SJS) include redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swelling and the signs of toxic epidermal necrolysis (TEN) include redness, blistering and/or peeling of large areas of the skin. If you experience signs of Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), you should immediately stop taking PAXLOVID and consult your healthcare professional.

**Cholesterol-lowering medicines:** Before you take PAXLOVID tell your healthcare professional if you are taking a cholesterol-lowering medicine such as lovastatin or simvastatin. PAXLOVID may increase the amount of these medicines in your body. You should stop taking lovastatin / simvastatin at least 12 hours prior to starting PAXLOVID. You must not take these while you are taking PAXLOVID and for 5 days after stopping treatment.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**Do not take PAXLOVID if you are taking any of the medicines listed under the "Do not use PAXLOVID if:" section.** Taking PAXLOVID with these medicines may cause serious or life-threatening side effects.

**The following may also interact with PAXLOVID:**

- medicines used to treat erectile dysfunction, such as sildenafil, and tadalafil
- medicines used to treat pulmonary arterial hypertension, such as bosentan, riociguat or tadalafil

- medicines used to lower blood cholesterol, such as atorvastatin and rosuvastatin
- some medicines affecting the immune system, such as cyclosporin, everolimus, sirolimus and tacrolimus
- some medicines used to treat seasonal allergies and ear and eye infections, such as budesonide, dexamethasone, fluticasone propionate, prednisone, and triamcinolone
- medicines used to treat HIV and related infections, such as amprenavir, bictegravir, efavirenz, indinavir*, nelfinavir, saquinavir, didanosine*, rifabutin, tipranavir, delavirdine*, atazanavir, maraviroc, fosamprenavir, raltegravir, tenofovir, nevirapine, zidovudine emtricitabine and darunavir
- medicines used to treat depression, such as trazodone, desipramine and bupropion
- certain heart medicines, such as calcium channel antagonists including amlodipine, diltiazem, felodipine, nicardipine, nifedipine and verapamil
- medicines used to treat men with symptoms of an enlarged prostate such as tamsulosin
- medicines used to correct heart rhythm, such as systemic digoxin and lidocaine, disopyramide and mexiletine
- medicines used to treat heart or blood vessel problems such as aliskiren, and vorapaxar
- certain blood thinners such as apixaban, clopidogrel, dabigatran, ticagrelor and warfarin
- antifungals, such as ketoconazole, isavuconazonium sulfate and itraconazole
- morphine-like medicines used to treat severe pain, such as methadone and meperidine
- certain antibiotics, such as rifabutin, erythromycin and clarithromycin
- antibiotics used in the treatment of tuberculosis, such as rifampin
- bronchodilators used to treat asthma, such as theophylline
- medicines used to treat cancer, such as abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, nilotinib,vincristine and vinblastine
- medicines used for low blood platelet count, such as fostamatinib
- some anticonvulsants, such as clonazepam, divalproex, lamotrigine and ethosuximide
- some narcotic analgesics, such as fentanyl in all forms, hydrocodone, oxycodone, meperidine, tramadol and propoxyphene
- quetiapine used to treat schizophrenia, bipolar disorder and major depressive disorder
- medicines used to treat hepatitis C, such as simeprevir, glecaprevir/pibrentasvir, ombitasvir/paritaprevir and ritonavir with or without dasabuvir*, elbasvir/grazoprevir, and sofosbuvir/velpatasvir/voxilaprevir
- some sedatives or medicines to treat anxiety, such as buspirone, clorazepate, diazepam, flurazepam and zolpidem
- stimulants, such as methamphetamine
- medicines used to treat pain associated with endometriosis, such as elagolix
- medicines used to treat depression, such as amitriptyline, clomipramine, fluoxetine, imipramine, maprotiline*, nefazodone*, nortriptyline, paroxetine, sertraline, trimipramine, venlafaxine
- medicines used to treat nausea and vomiting, such as dronabinol*
- medicines used to treat pneumonia, such as atovaquone
- medicines used as a sedative and medicines used to help you sleep (hypnotics), such as estazolam*
- medicines used to treat increased pressure in the eye, such as timolol
- medicines used to lower blood pressure, such as metoprolol
- medicines used to prevent organ rejection after a transplant, such as everolimus, sirolimus

- medicines used to treat certain mental health and mood disorders (including schizophrenia and bipolar disorder), such as aripiprazole, brexpiprazole, cariprazine, clozapine, iloperidone*, lumateperone*, perphenazine, pimavanserin*, risperidone, suvorexant*, and thioridazine*
- medicines used as hormonal contraceptives containing ethinyl estradiol ("the pill")
- medicines used to treat cystic fibrosis such as ivacaftor, elexacaftor/tezacaftor/ivacaftor and tezacaftor/ivacaftor
- medicines used to control blood sugar levels such as saxagliptin
- medicines used to treat rheumatoid arthritis and psoriatic arthritis such as tofacitinib and upadacitinib
- medicines used to treat malaria such as quinine
- medicines used to treat symptoms of an overactive bladder such as darifenacin

* Product is not or no longer marketed in Canada.

**How to take PAXLOVID:**

- PAXLOVID consists of two medicines co-packaged together:
    - nirmatrelvir (pink tablet)
    - ritonavir (white tablet)
- **You must always take the nirmatrelvir tablet(s) at the same time as the ritonavir tablet.**
- Always take PAXLOVID exactly as your healthcare professional has told you to.
- Check with your healthcare professional if you are not sure.
- You can take PAXLOVID with or without food.
- Swallow the tablets whole. Do not break, chew or crush the tablets.
- You must take PAXLOVID for 5 days in a row. Complete the entire 5-day treatment with PAXLOVID.
- Even if you feel better, do not stop taking PAXLOVID without talking to your healthcare professional first.
- Talk to your healthcare professional if you do not feel better or if you feel worse after 5 days.
- If you have kidney problems, talk to your healthcare professional. You may need to take a lower dose.

**Usual dose:**

Adults:
Take 2 pink nirmatrelvir tablets and 1 white ritonavir tablet. Take these 3 tablets at the same time, twice a day (in the morning and again in the evening) for 5 days.

**Dose for patients with moderate kidney impairment:**

**If you have kidney problems, talk to your healthcare professional. You may need to take a lower dose.**

Adults with moderate kidney impairment:
Take 1 pink nirmatrelvir tablet and 1 white ritonavir tablet. Take both tablets at the same time, twice a day (in the morning and again in the evening) for 5 days.

**Overdose:**

If you think you, or a person you are caring for, have taken too much PAXLOVID, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss taking your dose and it:

- is **within 8 hours** of the time it is usually taken, take it as soon as you remember.
- has been **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.

**What are possible side effects from using PAXLOVID?**

These are not all the possible side effects you may have when taking PAXLOVID. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- altered sense of taste
- diarrhea
- muscle pain
- vomiting
- high blood pressure
- headache
- abdominal pain
- nausea
- general feeling of discomfort

Not many people have taken PAXLOVID. Serious and unexpected side effects may happen. PAXLOVID is still being studied, so it is possible that all the side effects are not known at this time.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **Common** | | | |
| **High blood pressure** | | **X** | |
| **Severe allergic reaction:** skin rash, hives, itching of the skin, swelling under the skin, swelling of the mouth, lips, tongue, face and extremities, swelling and tightness of the throat, hoarseness, low blood pressure, fainting, weakness, difficulty in swallowing or breathing. | | | **X** |
| **Rare** | | | |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **Stevens-Johnson syndrome (SJS) (severe skin rash):** redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swelling. | | | **X** |
| **Toxic Epidermal Necrolysis (TEN) (severe skin reaction):** redness, blistering and/or peeling of large areas of the skin. | | | **X** |
| **Liver problems:** yellow skin or whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, abdominal pain, pale stool, or dark coloured urine. | | **X** | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:** Store at room temperature 15°C to 30°C.

Keep out of reach and sight of children.

**If you want more information about PAXLOVID:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

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