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

Submission Control Number: 259186

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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	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	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of PAXLOVID and potential loss of virologic response. In addition, 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	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 pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias.
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine[a],	Potential for serious and/or life-threatening reactions, such as acute ergot toxicity
	methylergonovine[a]	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 classof protease inhibitors.
Lipid-modifying Agents HMG-CoA Reductase Inhibitors Microsomal Triglyceride Transfer Protein (MTTP) Inhibitor	lovastatin, simvastatin lomitapide	Potential for serious reactions, such as risk of myopathy including rhabdomyolysis. 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.
PDE5 Inhibitors	sildenafil[b], only when used for the treatment of pulmonary arterial hypertension (PAH) 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. 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.

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 coadministration 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
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antimycobacterial: rifampin
- Herbal products: St. John's Wort (*hypericum perforatum*)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

The daily blister contains two separated parts each containing 2 tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose. Therefore, patients with **moderate renal impairment** should be alerted on the fact that **only one tablet of Nirmatrelvir** with the tablet of ritonavir should be taken every 12 hours. (see **4 DOSAGE AND ADMINISTRATION**)

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

- Renal Impairment

  Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment (see **10 CLINICAL PHARMACOLOGY, 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 nirmatrelvir and 100 mg ritonavir twice daily for 5 days**. Healthcare professionals should counsel patients about renal dosing instructions.

  The daily blister contains two separated parts each containing 2 tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose. Therefore, patients with moderate renal impairment should be alerted on the fact that only **one tablet of nirmatrelvir** with the tablet of ritonavir should be taken **every 12 hours**.

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

- 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 **7 WARNINGS AND PRECAUTIONS**).

- 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

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 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics**).

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 (co-packaged for use)	Nirmatrelvir Tablet (pink): 150mg	Tablet core: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate Film coat: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol and titanium dioxide
	Ritonavir Tablet (white): 100mg	Tablet core: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. 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.

- Nirmatrelvir tablets, 150 mg are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.
- Ritonavir tablets, 100 mg are white film-coated ovaloid tablets debossed with the "a" logo and the code NK.

Nirmatrelvir tablets and ritonavir tablets are supplied in separate cavities within the same child resistant blister card. Each carton contains 30 tablets divided in 5 daily-dose blister cards. Each daily blister card contains 4 nirmatrelvir tablets (150 mg each) and 2 ritonavir tablets (100 mg each) and indicates which tablets need to be taken in the morning and evening.

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**).

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.

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 8 times higher than clinical exposure at the authorized human dose of PAXLOVID. Ritonavir produced no effects on fertility in rats (see **16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity**).

- **Teratogenic risk**

  There are no available 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. 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 **16 NON-CLINICAL TOXICOLOGY, 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 no available 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 10 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 **16 NON-CLINICAL TOXICOLOGY**, **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 **16 NON-CLINICAL TOXICOLOGY**, **Reproductive and Developmental Toxicity**).

7.1.2 Breast-feeding

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 8 times higher than clinical exposures at the authorized human dose of PAXLOVID (see

16 NON-CLINICAL TOXICOLOGY, 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 breast-feeding 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 2,224 symptomatic adult subjects 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either PAXLOVID (n=1,109) or placebo (n=1,115). Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. PAXLOVID [300 mg nirmatrelvir (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 (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%).

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 = 1109 (%)	Placebo n = 1115 (%)
Nervous system disorders		
Dysgeusia	5.6	0.3
Headache	1.4	1.3
Gastrointestinal		
Diarrhoea	3.1	1.6
Vomiting	1.1	0.8

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

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**).

9.4 Drug-Drug Interactions

Potential for PAXLOVID to Affect Other Drugs

PAXLOVID is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. 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 P450 3A (CYP3A) and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents 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 also inhibits CYP2D6 to a lesser extent. Co-administration of substrates of CYP2D6 with ritonavir could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2B6 as well as other enzymes, including 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.

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 PAXLOVID therapeutic effect.

Established and Other Potentially Significant Drug Interactions

Table 4 provides listing of clinically significant drug interactions, including contraindicated drugs. Drugs listed in Table 4 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The healthcare professional should consult appropriate references for comprehensive information (see **2 CONTRAINDICATIONS**).

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 expected in the presence of ritonavir (600 mg twice daily). Therefore, alfuzosin is contraindicated with PAXLOVID (see **2 CONTRAINDICATIONS**).

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
Analgesics, Narcotic:		
fentanyl tramadol propoxyphene[a]	↑ fentanyl ↑ tramadol ↑ propoxyphene	Ritonavir inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl, tramadol, and propoxyphene. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when ritonavir is co-administered with fentanyl, including extended-release, transdermal or transmucosal preparations. Use tramadol and propoxyphene with caution, dose reduction of these drugs may be needed.
methadone	↓ methadone	Dosage increase of methadone may be considered.
Anesthetic:		
meperidine	↓ meperidine ↑ 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	↑ antiarrhythmics	Plasma concentrations of these drugs are expected to increase by co-administration withritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed.
amiodarone, bepridil[a], dronedarone, flecainide, propafenone, quinidine[a]	↑ antiarrhythmics	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:		
fusidic acid	↑ fusidic acid ↑ ritonavir	Coadministration of protease inhibitors, including ritonavir with fusidic acid is expectedto increase fusidic acid, as well as the proteaseinhibitor concentration in plasma (see **2 CONTRAINDICATIONS**).

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
Anticancer agents:		
abemaciclib, apalutamide, dasatinib, encorafenib, ibrutinib, 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. Coadministration of ritonavir with ibrutinib is not recommended due to expected increase inibrutinib exposure that could potentially resultin a risk of tumor lysis syndrome. 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). Coadministration of encorafenib with ritonavir should be avoided due to potential increase in encorafenib exposure potentially increasing the 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. 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). Concomitant use of ritonavir with apalutamide is contraindicated. 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). Coadministration of ritonavir with neratinib is contraindicated due to expected increase in neratinib exposure (see **2 CONTRAINDICATIONS**).
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**). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
		the venetoclax dose by at least 75% when used with strong CYP3A inhibitors (see VENCLEXTA Product Monograph).
Anticoagulants:		
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. PAXLOVID and rivaroxaban should not be used concomitantly (see **2 CONTRAINDICATIONS**).
warfarin	↓ R-warfarin ↓ ↑ S-warfarin	Initial frequent monitoring of the INR (International Normalized Ratio) during ritonavir and warfarin co-administration is indicated.
Anticonvulsants:		
clonazepam ethosuximide divalproex lamotrigine	↑ clonazepam ↑ ethosuximide ↓ divalproex ↓ 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. 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.
carbamazepine, phenobarbital, phenytoin	↑ carbamazepine ↓ phenytoin ↓ ritonavir ↓nirmatrelvir	Co-administration of PAXLOVID with carbamazepine, phenobarbital or phenytoin is contraindicated (see **2 CONTRAINDICATIONS**)
Antidepressants:		
amitriptyline, clomipramine, fluoxetine, imipramine, maprotiline, nefazodone, 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	Bupropion is primarily metabolized by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir decreases bupropion levels.

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
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	↑ dronabinol	Plasma concentrations of dronabinol are expected to increase by co-administration withritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of dronabinol may be needed.
Antifungal:		
ketoconazole itraconazole	↑ ketoconazole ↑ itraconazole	High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antigout:		
colchicine	↑ colchicine	For patients with renal and/or hepatic impairment: • 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**). For patients with normal renal and/or hepatic function: • *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. • *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 onceevery other day.

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
		• *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	↑ clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the doseof clarithromycin should be reduced by 75%. No dose adjustment for patients with normal renal function is necessary.
Antimycobacterial:		
rifabutin	↑ rifabutin and rifabutin metabolite ↓ 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.
rifampin	↓ ritonavir ↓nirmatrelvir	Co-administration of PAXLOVID with rifampin is contraindicated (see **2 CONTRAINDICATIONS**).
Antiparasitics:		
atovaquone	↓ atovaquone	Plasma concentrations of atovaquone are expected to decrease by co-administration withritonavir. Therefore, PAXLOVID should be used with caution, dose increase of atovaquone may be needed.
quinine	↑ quinine	Plasma concentrations of quinine are expectedto increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of quinine may be needed.
Anxiolytics/Sedative/Hypnotics:		
midazolam, oral[a]	↑ 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 of oral midazolam with PAXLOVID is contraindicated (see **2 CONTRAINDICATIONS**).
midazolam, parenteral	↑ midazolam	Concomitant use of parenteral midazolam with ritonavirmay increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
		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.
Beta-blockers:		
metoprolol, timolol	↑ beta-blockers	Plasma concentrations of these drugs are expected to increase by co-administration withritonavir. 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 beconsidered.
Calcium channel blockers:		
diltiazem, nifedipine, verapamil	↑ calcium channel blockers	Plasma concentrations of these drugs are expected to increase by co-administration withritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed.
Corticosteroids:		
fluticasone propionate, budesonide, triamcinolone	↑ fluticasone ↑ budesonide ↑ 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. 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.

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
dexamethasone prednisone	↑dexamethasone ↓ ritonavir ↑ prednisone	Dexamethasone, which increases CYP3A activity, would be expected to increase the clearance of ritonavir resulting in decreased ritonavir plasma concentrations. 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.
Endothelin receptor antagonist:		
bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of PAXLOVID. Refer to the bosentan product label for further information.
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 label for dosing information with strong CYP3A4 inhibitors.
HCV-Antiviral Agents		
HCV Combination Drug:		
ombitasvir/paritaprevir/ ritonavir with or without dasabuvir[a]	↑ paritaprevir	Exposures of paritaprevir may be increased when co-administered with ritonavir, therefore,co-administration is not recommended.
HCV Protease Inhibitors:		
simeprevir[a]	↑ simeprevir	A pharmacokinetic study demonstrated that concomitant administration of simeprevir 200 mg once daily with ritonavir 100 mg twicedaily resulted in an increase in simeprevir concentrations. It is not recommended to co-administer PAXLOVID with simeprevir.

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
glecaprevir/pibrentasvir	↑ glecaprevir	Coadministration with ritonavir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.
HIV-Antiretroviral Agents		
HIV Protease Inhibitors:		
fosamprenavir	↑ amprenavir (↑ 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 ritonavir200 mg once daily.
atazanavir	↑ atazanavir (↑ 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. Refer to the atazanavir Product Monograph fordetails on co-administration of atazanavir 300 mg once daily, with ritonavir 100 mg once daily.
darunavir	↑ darunavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	Refer to the darunavir Product Monograph fordetails on co-administration of darunavir 600 mg twice daily with ritonavir 100 mg twice daily.
indinavir[a]	↑ indinavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	Alterations in concentrations are noted when reduced doses of indinavir are co-administeredwith reduced dose of ritonavir. The safety and efficacy of this combinationhave not yet been established. 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.
saquinavir	↑ saquinavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	The recommended dosage regimen is saquinavir 1000 mg with ritonavir 100 mg twicedaily taken within 2 hours after a meal. Dose adjustment may be needed if other HIV-protease inhibitors are used in combinationwith saquinavir and ritonavir. 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. In some cases, co-administration of saquinavirand ritonavir has led to severe adverse events,mainly diabetic ketoacidosis, and liver disorders, especially

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
		in patients with pre- existing liver disease. Refer to the saquinavir Product Monograph for prescribing information.
tipranavir	↑ tipranavir (↑ AUC, ↑ Cmax, ↑ Cmin)	Refer to the tipranavir Product Monograph fordetails on co-administration of tipranavir 500 mg twice daily with ritonavir 200 mg twicedaily.
Nucleoside Reverse Transcriptase Inhibitors:		
didanosine	↓ 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.
Non-Nucleoside Reverse Transcriptase Inhibitors:		
Delavirdine[a]	↑ ritonavir ↔ delavirdine	When used in combination with delavirdine, a dose reduction of ritonavir should be considered. Based on comparison to historicaldata, 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.
Integrase Inhibitor:		
raltegravir	↓ raltegravir	A pharmacokinetic study showed that co-administration of ritonavir 100 mg twice dailyand raltegravir 400 mg single dose resulted in a reduction in raltegravir plasma concentration.
CCR5 Antagonist:		
maraviroc	↑ maraviroc (↑ 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 twicedaily with ritonavir.
Hypolipidemics, HMG-CoA Reductase Inhibitors:		
lovastatin, simvastatin	↑ lovastatin, simvastatin	The HMG-CoA reductase inhibitors simvastatinand lovastatin are highly dependent on CYP3A for

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
		metabolism, thus concomitant use of ritonavirwith simvastatin or lovastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis (see **2 CONTRAINDICATIONS**).
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. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated.
atorvastatin, rosuvastatin	↑ 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. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. Use the lowest doses of atorvastatin or rosuvastatin with careful monitoring for signs and symptoms of myopathy or rhabdomyolysis. If treatment withan HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.
Immunosuppressants:		
cyclosporine, everolimus, tacrolimus, rapamycin[a]	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ritonavir.
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).
Neuroleptics/Antipsychotics:		
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,

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
		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/orlife-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 beenreported with CYP3A inhibitors. PAXLOVID should not be used in combination with quetiapine. Monitoring and dose reduction may be required if necessary.
Oral Contraceptive or Patch Contraceptive:		
ethinyl estradiol	↓ ethinyl estradiol	Dosage increase or alternate contraceptivemeasures should be considered.
PDE5 Inhibitors:		
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. Use of PDE5 Inhibitors for Erectile Dysfunction Sildenafil may be used with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Tadalafil may be used with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Vardenafil should not be used with PAXLOVID (see **2 CONTRAINDICATIONS**). Use of PDE5 Inhibitors for Pulmonary Arterial Hypertension Coadministration of PAXLOVID and tadalafil forthe treatment of pulmonary arterial hypertension is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentrationof PAXLOVID or Concomitant Drug	Clinical Comment
		The use of sildenafil or vardenafil is contraindicated with PAXLOVID (see **2 CONTRAINDICATIONS**).
Stimulants:		
methamphetamine	↑ methamphetamine	Ritonavir dosed as a pharmacokinetic enhancer is not expected toresult in any clinically meaningful increases inCYP2D6 substrates. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed.
a. Product not marketed in Canada. ↑ Indicates increase; ↓ indicates decrease; ↔ indicates no change.		

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.

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir, thereby supporting a twice daily administration regimen.

Upon oral administration of nirmatrelvir/ritonavir, the increase in systemic exposure appears to be less than dose proportional up to 750 mg as a single dose and up to 500 mg twice daily as multiple doses.

Twice daily dosing over 10 days achieved steady-state on Day 2 with approximately 2-fold accumulation. The pharmacokinetic properties of nirmatrelvir; ritonavir are displayed in Table 5.

Table 5: 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]
Distribution		
% bound to human plasma proteins	69%	98-99%
Blood-to-plasma ratio	0.60	0.14[c]
V_z/F (L), mean	104.7 [b]	112.4 [b]
Elimination		
Major route of elimination	Renal elimination[d]	Hepatic metabolism
Half-life ($t_{1/2}$) (hr), mean	6.05[a]	6.15[a]
Oral clearance (CL/F), mean	8.99[a]	13.92[a]
Metabolism		
Metabolic pathways	Minimal[d]	Major CYP3A4, Minor CYP2D6
Excretion		
% drug-related material in feces	49.6%[e]	86.4%[f]
% drug-related material in urine	35.3%[e]	11.3%[f]

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. 300 mg nirmatrelvir (oral suspension formulation) and 100 mg ritonavir (tablet formulation) administered together twice a day for 3 days.
c. Red blood cell to plasma ratio.
d. Nirmatrelvir is a CYP3A4 substrate but when dosed with ritonavir metabolic clearance is minimal.
e. 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.
f. 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 6.

Table 6: 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:

An exploratory study in 4 healthy volunteers showed that dosing with a high-fat high-calorie meal modestly increased the exposure of nirmatrelvir (approximately 15% increase in mean C_{max} and 1.6% increase in mean AUC_{last}) relative to fasting conditions following administration of a suspension formulation (250mg) of nirmatrelvir co-administered with ritonavir (100 mg) tablets.

Distribution

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

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.

Drug Interaction Studies Conducted with Nirmatrelvir

In vitro data indicates that nirmatrelvir is a substrate for human MDR1 (P-gp) and 3A4, but not a substrate for human BCRP, MATE1, MATE2K, NTCP, OAT1, OAT2, OAT3, OCT1, OCT2, PEPT1, OATPs 1B1, 1B3, 2B1, or 4C1.

Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 in vitro at clinically relevant concentrations. There is a potential for nirmatrelvir to inhibit P-glycoprotein (also known as MDR1) and OATP1B1 at clinically relevant concentrations. (see **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions**). Nirmatrelvir has the potential to reversibly and time-dependently inhibit CYP3A4 and inhibit MDR1 (P-gp).

Nirmatrelvir does not induce any CYPs at clinically relevant concentrations.

The effects of co-administration of PAXLOVID with itraconazole (CYP3A inhibitor) and carbamazepine (CYP3A inducer) on the nirmatrelvir AUC and C_{max} are summarized in Table 4 (**effect of other drugs on nirmatrelvir**).

Table 7: Drug Interactions: Pharmacokinetic Parameters for Nirmatrelvir in the Presence of the Co-administered Drugs

	Dose (Schedule)			Ratio (in combination with Co-administered drug/alone) of Nirmatrelvir Pharmacokinetic Parameters (90% CI); No Effect=100	
Co-administered Drug	**Co-administered Drug**	**Nirmatrelvir/ Ritonavir**	**N**	**C_{max}**	**AUC[a]**
Carbamazepine[b]	300 mg twice daily (16 doses)	300 mg/100 mg twice daily (5 doses)	9	56.82 (47.04, 68.62)	44.50 (33.77, 58.65)
Itraconazole	200 mg once daily (8 doses)	300 mg/100 mg twice daily (5 doses)	11	118.57 (112.50, 124.97)	138.82 (129.25, 149.11)

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

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

b. Carbamazepine titrated up to 300 mg twice daily on Day 8 through Day 15 (e.g., 100 mg twice daily on Day 1 through Day 3 and 200 mg twice daily on Day 4 through Day 7).

Drug Interaction Studies Conducted with Ritonavir

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

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

Special Populations and Conditions

- **Age/Gender** The pharmacokinetics of nirmatrelvir/ritonavir based on age and gender have not been evaluated.
- **Pediatrics** The pharmacokinetics of nirmatrelvir/ritonavir in patients less than 18 years of age have not been evaluated.
- **Ethnic Origin** Systemic exposure in Japanese participants was numerically lower but not clinically meaningfully different than those in Western participants
- **Hepatic Insufficiency** The pharmacokinetics of nirmatrelvir ritonavir have not been evaluated in patients with hepatic impairment. A single oral dose of 100 mg nirmatrelvir enhanced with 100 mg ritonavir at -12 hours, 0 hours, 12 hours and 24 hours in subjects with moderate hepatic impairment resulted in similar exposures compared to subjects with normal hepatic function. Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Table 8: Impact of Hepatic Impairment on Nirmatrelvir/Ritonavir Pharmacokinetics

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

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

- **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 9: 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

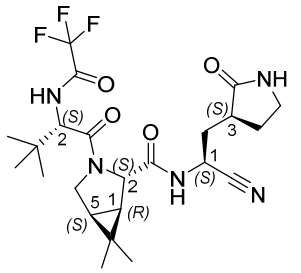
Drug Substance

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:



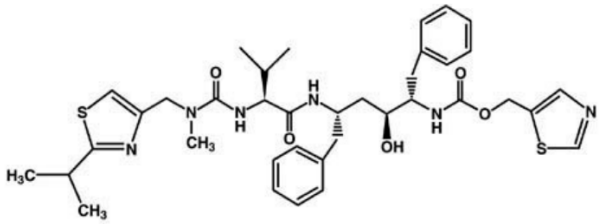
Physicochemical properties: nirmatrelvir is a white to pale coloured powder with a melting onset of approximately 192 °C. Nirmatrelvir is soluble in 1-Butanol, Methyl isobutyl ketone (MIBK), and Isopropyl acetate. It is sparingly soluble in n-Propyl acetate, n-Butyl acetate, and Anisole, and very slightly 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 interim analysis of EPIC-HR, a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. Eligible subjects 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. Subjects with COVID-19 symptom onset of ≤5 days were included in the study. Subjects were randomized (1:1) to receive PAXLOVID (nirmatrelvir/ritonavir 300 mg/100 mg) or placebo orally every 12 hours for 5 days. The primary efficacy endpoint was the proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28. The study excluded individuals with a history of prior COVID-19 infection or vaccination. The analysis was conducted in the modified intent-to treat (mITT) analysis set (all treated subjects with onset of symptoms ≤3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), the mITT1 analysis set (all treated subjects with onset of symptoms ≤5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment), and the mITT2 analysis set (all treated subjects with onset of symptoms ≤5 days). The primary SARS-CoV-2 variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I

A total of 1,361 participants were randomised to receive either PAXLOVID or placebo. At baseline, mean age was 45 years; 52% were male; 63% were White, 5% were Black, 48% were Hispanic or Latino and 20% were Asian; 63% of participants had onset of symptoms ≤ 3 days from initiation of study treatment; 44% of participants were serological negative at baseline. The mean (SD) baseline viral load was 4.71 log10 copies/mL (2.78); 27% of participants had a baseline viral load of > 10^7 (units); 8.2% of participants either received or were expected to receive COVID-19 therapeutic monoclonal antibody treatment at the time of randomisation and were excluded from the mITT and mITT1 analyses.

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

At time of the interim analysis, 389 participants in the PAXLOVID group and 385 participants in the placebo group were included in the mITT analysis set. PAXLOVID significantly reduced ($p<0.0001$) the proportion of participants with COVID-19 related hospitalisation or death through Day 28 by 89.1%, compared with placebo, in adult participants with symptom onset ≤ 3 days who were at increased risk of progression to severe disease. No deaths were reported in the PAXLOVID group compared with 7 deaths in the placebo group. The proportions of participants who discontinued treatment due to an adverse event were 2.4% in the PAXLOVID group and 4.3% in the placebo group.

Table 10: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT analysis set

	PAXLOVID 300 mg/100 mg	Placebo
Number of Patients (%)	(N=389)	(N=385)
Patients with hospitalisation or death[a] (%)	3 (0.8%)	27 (7.0%)
Estimated proportion over 28 days [95% CI], %	0.78 (0.25, 2.39)	7.09 (4.92, 10.17)
Reduction relative to placebo [95% CI]* p-value**	-6.32 (-9.04, -3.59)	

*95% two-sided confidence interval unadjusted for multiplicity. The 95% two-sided confidence interval adjusted for multiplicity for the interim analysis is [-10.61% to -2.02%].
**Two-sided significance level of 0.002.
Abbreviations: CI=confidence interval; mITT=modified intent-to-treat. 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 monoclonal antibody treatment, and were treated ≤ 3 days after COVID-19 symptom onset.
a. Covid-19 related hospitalisation or death from any cause.

Table 11: Progression of COVID-19 (hospitalisation or death) through Day 28 in symptomatic adults at increased risk of progression to severe illness; mITT1 patients with treatment initiated > 3 days and <5 days from symptom onset

	PAXLOVID 300 mg/100 mg	Placebo
Number of Patients (%)	(N=218)	(N=227)
Patients with hospitalisation or death[a] (%)	3 (1.4%)	14 (6.2%)
Estimated proportion over 28 days [95% CI], %	1.40 (0.45, 4.29)	6.19 (3.72, 10.24)
Reduction relative to placebo [95% CI] p-value	-4.79 (-8.31, -1.28) 0.0076	

Abbreviations: CI=confidence interval; mITT1=A modified intent-to-treat analysis set that includes 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 monoclonal antibody treatment and were treated ≤ 5 days after COVID-19 symptom onset.
a. Covid-19 related hospitalisation or death from any cause.

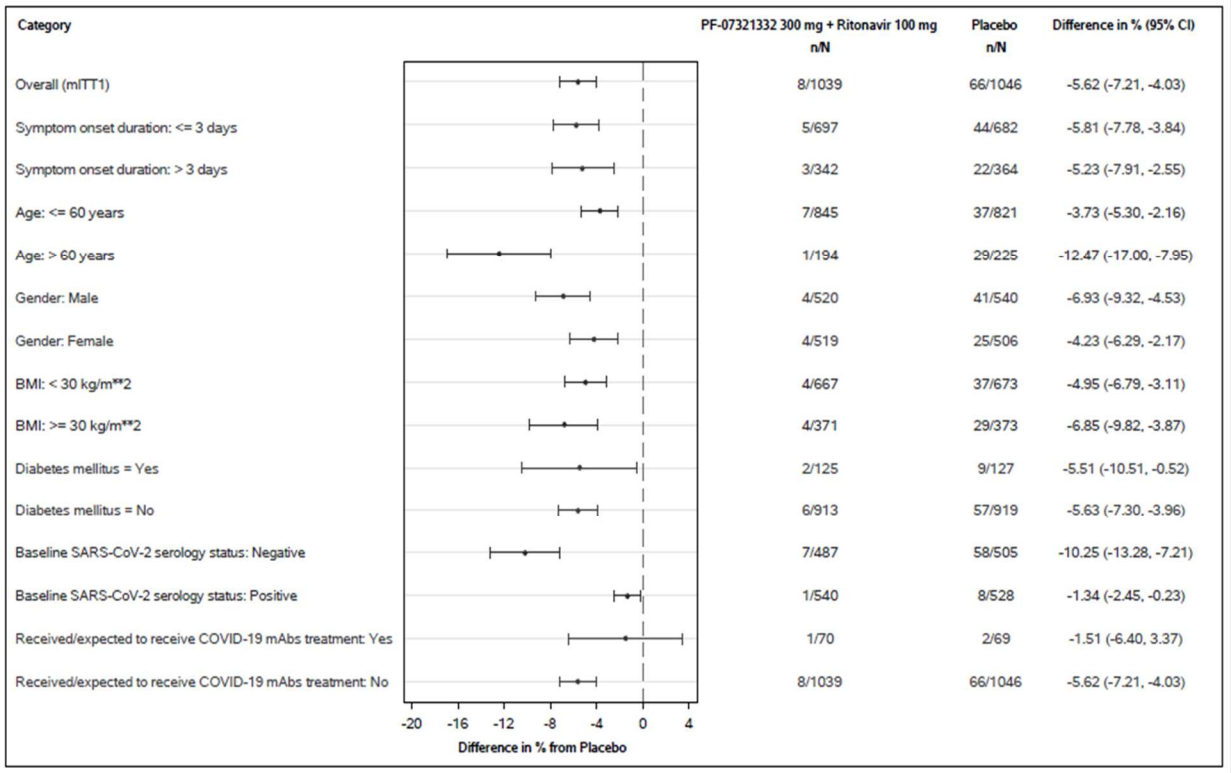
Consistent results were observed in interim results in the mITT2 analysis population.

Topline Results

The topline results from the final analysis included a total of 2246 subjects. The final results in the mITT, mITT1 and mITT2 analysis sets were consistent those was observed in the interim analysis. In the final analysis a total of 1,379 subjects were included in the mITT analysis population. The event rates were 5/697 (0.72%) in the PAXLOVID group, and 44/682 (6.45%) in the placebo group.

Similar trends have been observed across subgroups of subjects (see Figure 1). These subgroup analyses from the topline final analysis are considered exploratory.

Figure 1: Subjects with COVID-19-Related-Hospitalization or Death from Any Cause Through Day 28 (Protocol C4671005)



N=number of participants in the category of the analysis set.
All categories are based on mITT1 population except for COVID-19 mAb treatment which is based on mITT2 population.
Seropositivity was defined if results were positive in either Elecsys anti SARS CoV-2 S or Elecsys SARS CoV-2 (N) assay.
The difference of the proportions in the 2 treatment groups and its 95% confidence interval based on Normal approximation of the data are presented.

Relative to placebo, PAXLOVID treatment was associated with an approximately 0.9 $\log_{10}$ copies/mL greater decline in viral RNA levels in nasopharyngeal samples through Day 5, with similar results observed in the mITT, mITT1, and mITT2 analysis populations.

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 with EC_{50} and EC_{90} values of 62 nM and 181 nM, respectively, after 3 days of drug exposure.

Nirmatrelvir had similar cell culture antiviral activity (EC_{50} values ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta

(B.1.617.2), Lambda (C.37), and Mu (B.1.621) variants. The Beta (B.1.351) variant was the least susceptible tested variant with approximately 4-fold reduced susceptibility relative to the USA-WA1/2020 isolate.PF-07321332 showed antiviral activity against the Omicron variant with IC50 values of 70 nM and 23 nM in the HeLa-ACE2 and Vero-TMPRSS cells compared to the SARS-CoV-2 USA-WA1/2020 strain which had IC_{50} values of 207 nM and 38 nM in the same cell lines, respectively, using an immunostaining-based method.

Antiviral Resistance

Resistance *in vitro*

No information on antiviral resistance is currently available to PF-07321332 with SARS-CoV-2. Studies to evaluate selection of resistance to PF-07321332 with SARS-CoV-2 in cell culture and clinical studies have not been completed. Only in vitro resistance selection study with murine hepatitis virus (MHV)-3CL protease is available. It showed a 4.4- to 5-fold decrease in PF-07321332 susceptibility against mutant viruses with 5 mutations (P55L, S144A, T129M, T50K, P15A) in the MHV-3CL protease following 10 passages in cell culture. The clinical relevance for this to SARS-CoV-2 is not known.

Phenotypic assessments were conducted to characterize the impact of naturally occurring SARSCoV2 3CL polymorphisms on the activity of nirmatrelvir in a biochemical assay using recombinant 3CL protease. The clinical significance of these polymorphisms is unknown, and it is also unknown if results from the biochemical assay are predictive of antiviral activity in cell culture. The following 3CLpro amino acid substitutions were associated with reduced nirmatrelvir activity (i.e., higher Ki values): G15S (4.4-fold), H164N (6.4-fold), H172Y (233-fold), and Q189K (65.4-fold). In addition, SARS-CoV-2 3CLpro amino acid substitutions that have not been naturally observed were tested in biochemical assay. The following 3CLpro amino acid substitutions were associated with reduced nirmatrelvir activity (i.e., higher Ki values): Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). The clinical significance of these engineered 3CLpro substitutions is unknown. G15S is present in the Lambda variant, which did not have reduced susceptibility to nirmatrelvir (relative to USAWA1/2020) in cell culture.

Resistance *in vivo*

Limited SARS-CoV-2 sequencing data are available to characterize nirmatrelvir resistance in clinical trials. The SARS-CoV-2 3CL protease substitutions A260V (n=3) or A260T (n=1) emerged in 4% (4/97) of nirmatrelvir/ritonavir treated subjects in clinical trial EPIC-HR with available sequence analysis data. A260T and A260V substitutions are infrequent natural polymorphisms in publicly available SARS-CoV-2 sequences (as of Dec 5, 2021). In a biochemical assay, the A260V 3CL protease substitution did not reduce nirmatrelvir activity (fold-change <1).

Cross-resistance is not expected between nirmatrelvir and anti-SARS-CoV-2 monoclonal antibodies or remdesivir based on their different mechanisms of action.

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 authorized 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 authorized 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 proteinurea 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 authorized 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 authorized 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 authorized 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, there were no Nirmatrelvir-related effects on fertility and reproductive performance at doses up to 1000 mg/kg/day.

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 6 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 8 times higher than clinical exposures at the authorized 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 10 times higher than clinical exposures at the authorized 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 authorized human dose of PAXLOVID.

A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 is ongoing. 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 from PND 28 to PND 56. Of note, this PPND study is ongoing and so only interim data through PND 56 is currently available. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 8 times higher than clinical exposures at the authorized 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 5 times higher than clinical exposures at the authorized 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 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) approximately 4 times higher than exposure at the authorized 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 authorized 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 authorized 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 authorized 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 authorized 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
- Ritonavir (white tablet): 100 mg

Each carton contains 5 blister cards. Each blister card contains 6 tablets: 4 pink tablets (150 mg nirmatrelvir) and 2 white tablets (100 mg ritonavir).

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 high blood pressure
  - amiodarone, bepridil*, dronedarone, flecainide, propafenone, quinidine, used to treat irregular heartbeats
  - apalutamide, used for prostate cancer
  - astemizole* or terfenadine*, used to relieve allergy symptoms
  - cisapride*, used to relieve certain stomach problems
  - colchicine, when used in patients with kidney and/or liver problems, used to treat gout
  - ergotamine*, dihydroergotamine (used to treat headaches), ergonovine, methylergonovine* (used after labour and delivery)
  - fusidic acid, used as an antibiotic
  - lovastatin, lomitapide or simvastatin, used to lower cholesterol
  - lurasidone, pimozide, used to treat mental health problems
  - neratinib, used to treat breast cancer
  - ranolazine, used to treat chronic angina (chest pain)
  - rifampin and saquinavir, used to treat tuberculosis, should not be used together with ritonavir
  - rivaroxaban, used as an anticoagulant
  - salmeterol, used for asthma and chronic obstructive pulmonary disease
  - St. John's Wort (*Hypericum perforatum*), an herbal product used to treat depression
  - triazolam and midazolam* (oral or injected), used to relieve anxiety and/or trouble sleeping
  - PDE5 inhibitors vardenafil, used to treat erectile dysfunction, or sildenafil, used for the treatment of pulmonary arterial hypertension (PAH)

- voriconazole, used as an antifungal
- venetoclax during the dose initiation and during the ramp-up phase, used to treat chronic lymphocytic leukemia
- carbamazepine, phenobarbital, phenytoin used to treat seizures (epilepsy)

* 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 Contraception: 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 contraception while they are taking PAXLOVID. PAXLOVID may affect how birth control pills, patches and vaginal rings work. You should use alternate contraception or an additional barrier method such as a condom while you are taking PAXLOVID. 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.

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 tadalafil
- medicines used to treat pulmonary arterial hypertension, such as bosentan or tadalafil
- medicines used to lower blood cholesterol, such as atorvastatin and rosuvastatin
- some medicines affecting the immune system, such as cyclosporin, 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 AIDS and related infections, such as amprenavir, indinavir*, nelfinavir, saquinavir, didanosine*, rifabutin, tipranavir, delavirdine*, atazanavir, maraviroc, fosamprenavir, raltegravir, tenofovir and darunavir
- medicines used to treat depression, such as trazodone, desipramine and bupropion
- certain heart medicines, such as calcium channel antagonists including diltiazem, nifedipine and verapamil
- medicines used to correct heart rhythm, such as systemic lidocaine and digoxin
- antifungals, such as ketoconazole and itraconazole*
- morphine-like medicines used to treat severe pain, such as methadone and meperidine
- anticoagulants, such as warfarin
- certain antibiotics, such as rifabutin 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, dasatinib, encorafenib, ibrutinib, nilotinib,vincristine and vinblastine
- medicines used for low blood platelet count, such as fostamatinib
- some heart rhythm drugs, such as mexiletine and disopyramide
- some anticonvulsants, such as clonazepam, divalproex, lamotrigine and ethosuximide
- some narcotic analgesics, such as fentanyl in all forms, 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 or ombitasvir, paritaprevir and ritonavir with or without dasabuvir*
- 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
- 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 treat HIV, such as efavirenz
- medicines used to prevent organ rejection after a transplant, such as everolimus, rapamycin
- medicines used to treat certain mental/mood disorders such as schizophrenia, bipolar disorder, such as perphenazine, risperidone and thioridazine
- medicines used as hormonal contraceptives containing ethinyl estradiol ("the pill")

* Product is not or no longer marketed in Canada.

How to take PAXLOVID:

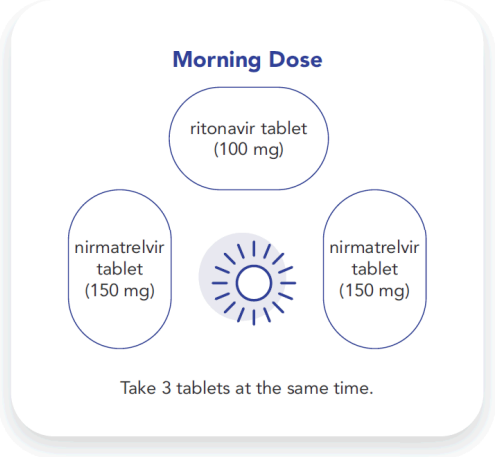
- PAXLOVID consists of two medicines co-packaged together:
    - nirmatrelvir (pink tablet)
    - ritonavir (white tablet)
- **You must always take the nirmatrelvir tablets at the same time as the ritonavir tablet.**
- Always take PAXLOVID exactly as your healthcare professional has told you to.

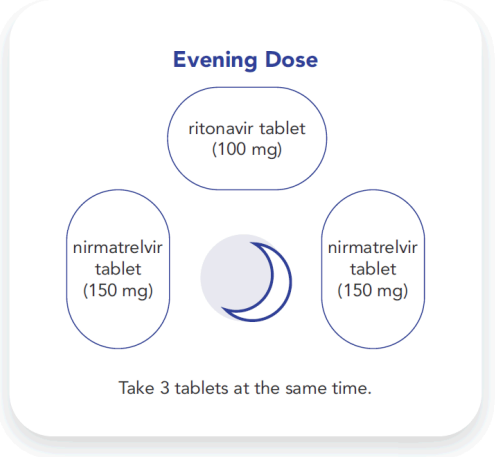
- Check with your healthcare professional if you are not sure.
- You can take PAXLOVID with or without food.
- Swallow the tablets whole. Do not break, chew or crush the tablets.
- You must take PAXLOVID for 5 days in a row. Complete the entire 5 day treatment with PAXLOVID.
- Even if you feel better, do not stop taking PAXLOVID without talking to your healthcare professional first.
- Talk to your doctor 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.

Each blister card shows your morning and evening dose, as follows:





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

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

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.

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 health 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.

This leaflet was prepared by Pfizer Canada ULC.

Last Revised January 17, 2022