

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

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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 , methylergonovine ^a	Potential for serious and/or life-threatening reactions, such as acute ergot toxicity characterized by vasospasm and tissue ischemia.
GI Motility Agent	cisapride ^a	Potential for serious and/or life-threatening reactions, such as cardiac arrhythmias.
 Herbal Products	St. John's wort (<i>Hypericum perforatum</i>)	May lead to loss of virologic response and possible resistance to PAXLOVID or to the class of protease inhibitors.
 Lipid-modifying Agents		
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for serious reactions, such as risk of myopathy including rhabdomyolysis.
Microsomal Triglyceride Transfer Protein (MTTP) Inhibitor	lomitapide	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.
<p>a. Product no longer marketed in Canada.</p> <p>b. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS for co-administration of sildenafil in patients with erectile dysfunction.</p> <p>c. See Table 4 for parenterally administered midazolam. Oral formulation of midazolam is not marketed in Canada.</p> <p>d. See Table 4 for coadministration of the maintenance dose of venetoclax.</p>		

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 $\geq 1\%$ 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 Concentration of 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 with ritonavir. 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 expected to increase fusidic acid, as well as the protease inhibitor concentration in plasma (see 2 CONTRAINDICATIONS).

Concomitant Drug Class: Drug Name	Effect on Concentration of PAXLOVID or Concomitant Drug	Clinical Comment
Anticancer agents:		
abemaciclib, apalutamide, dasatinib, encorafenib, ibrutinib, neratinib, nilotinib, vincristine, vinblastine	↑ anticancer agents	<p>Serum concentrations increase when co-administered with ritonavir resulting in the potential for increased incidence of adverse events, some of which may be serious.</p> <p>Coadministration of ritonavir with ibrutinib is not recommended due to expected increase in ibrutinib exposure that could potentially result in a risk of tumor lysis syndrome.</p> <p>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 dasatinib dose reduction should be considered (see SPRYCEL Product Monograph).</p> <p>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.</p> <p>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).</p> <p>Concomitant use of ritonavir with apalutamide is contraindicated.</p> <p>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).</p> <p>Coadministration of ritonavir with neratinib is contraindicated due to expected increase in neratinib exposure (see 2 CONTRAINDICATIONS).</p>
venetoclax	↑ venetoclax	<p>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).</p> <p>For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce</p>

Concomitant Drug Class: Drug Name	Effect on Concentration of 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 bupropion	↑ antidepressants ↓ bupropion	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 is primarily metabolized by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir decreases bupropion levels.

Concomitant Drug Class: Drug Name	Effect on Concentration of 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 with ritonavir. 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	<p><u>For patients with renal and/or hepatic impairment:</u></p> <ul style="list-style-type: none"> 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). <p><u>For patients with normal renal and/or hepatic function:</u></p> <ul style="list-style-type: none"> <i>Treatment of gout flares:</i> 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. <i>Prophylaxis of gout flares:</i> If the original colchicine regimen was 0.6 mg twice daily, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.3 mg twice daily, the regimen should be adjusted to 0.3 mg once every other day.

Concomitant Drug Class: Drug Name	Effect on Concentration of PAXLOVID or Concomitant Drug	Clinical Comment
		<ul style="list-style-type: none"> 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	<p>For patients with renal impairment, the following dosage adjustments should be considered:</p> <ul style="list-style-type: none"> 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 dose of clarithromycin should be reduced by 75%. <p>No dose adjustment for patients with normal renal function is necessary.</p>
Antimycobacterial:		
rifabutin	↑ rifabutin and rifabutin metabolite ↓ ritonavir	<p>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 may be necessary.</p> <p>Co-administration of PAXLOVID with rifampin is contraindicated (see 2 CONTRAINDICATIONS).</p>
rifampin	↓ ritonavir ↓ nirmatrelvir	
Antiparasitics:		
atovaquone	↓ atovaquone	<p>Plasma concentrations of atovaquone are expected to decrease by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose increase of atovaquone may be needed.</p> <p>Plasma concentrations of quinine are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of quinine may be needed.</p>
quinine	↑ quinine	
Anxiolytics/Sedative/Hypnotics:		
midazolam, oral ^a	↑ midazolam	<p>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).</p>
midazolam, parenteral	↑ midazolam	<p>Concomitant use of parenteral midazolam with ritonavir may increase plasma concentrations of midazolam. Co-administration should be done in a setting which ensures close clinical monitoring and</p>

Concomitant Drug Class: Drug Name	Effect on Concentration of 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 with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed.
Bronchodilator:		
theophylline	↓ theophylline	Increased dosage of theophylline may be required; therapeutic monitoring should be considered.
Calcium channel blockers:		
diltiazem, nifedipine, verapamil	↑ calcium channel blockers	Plasma concentrations of these drugs are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed.
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 Concentration of 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-administering 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 twice daily resulted in an increase in simeprevir concentrations. It is not recommended to co-administer PAXLOVID with simeprevir.

Concomitant Drug Class: Drug Name	Effect on Concentration of 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 ritonavir 200 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 for details 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 for details 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-administered with reduced dose of ritonavir. The safety and efficacy of this combination have 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 twice daily taken within 2 hours after a meal. Dose adjustment may be needed if other HIV-protease inhibitors are used in combination with saquinavir and ritonavir. 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 saquinavir and ritonavir has led to severe adverse events, mainly diabetic ketoacidosis, and liver disorders, especially



Concomitant Drug Class: Drug Name	Effect on Concentration of 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, ↑ C _{max} , ↑ C _{min})	Refer to the tipranavir Product Monograph for details on co-administration of tipranavir 500 mg twice daily with ritonavir 200 mg twice daily.
Nucleoside Reverse Transcriptase Inhibitors:		
didanosine	↓ 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 historical data, the pharmacokinetics of delavirdine did not appear to be affected by ritonavir. The safety and efficacy of this combination (delavirdine/ritonavir) have not been established.
efavirenz	↑ efavirenz	In healthy volunteers receiving 500 mg ritonavir twice daily with efavirenz 600 mg once daily, the steady state AUC was increased by 21%. An associated increase in the AUC of ritonavir of 17% was observed.
Integrase Inhibitor:		
raltegravir	↓ raltegravir	A pharmacokinetic study showed that co-administration of ritonavir 100 mg twice daily and raltegravir 400 mg single dose resulted in a reduction in raltegravir plasma concentration.
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 twice daily with ritonavir.
Hypolipidemics, HMG-CoA Reductase Inhibitors:		
lovastatin, simvastatin	↑ lovastatin, simvastatin	The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A for



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lomitapide	↑ lomitapide	metabolism, thus concomitant use of ritonavir with simvastatin or lovastatin is contraindicated due to an increased risk of myopathy including rhabdomyolysis (see 2 CONTRAINDICATIONS). 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 with an 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 perphenazine, risperidone, thioridazine ^a	↑ lurasidone ↑ neuroleptics	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. Co-administration of lurasidone with PAXLOVID is contraindicated (see 2 CONTRAINDICATIONS). 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 Concentration of PAXLOVID or Concomitant Drug	Clinical Comment
<p>pimozide</p> <p>quetiapine</p>	<p>↑ pimozide</p> <p>↑ quetiapine</p>	<p>PAXLOVID should be used with caution, dose reduction of these drugs may be needed.</p> <p>Co-administration of PAXLOVID with pimozide is contraindicated as it may lead to serious and/or life-threatening reactions, such as cardiac arrhythmias (see 2 CONTRAINDICATIONS).</p> <p>Due to inhibition of CYP3A by PAXLOVID (ritonavir), co-administration of PAXLOVID with quetiapine may result in increased quetiapine concentrations. Serious and life-threatening quetiapine-related adverse reactions have been reported with CYP3A inhibitors. PAXLOVID should not be used in combination with quetiapine. Monitoring and dose reduction may be required if necessary.</p>
Oral Contraceptive or Patch Contraceptive:		
ethinyl estradiol	↓ ethinyl estradiol	Dosage increase or alternate contraceptive measures should be considered.
PDE5 Inhibitors:		
sildenafil, tadalafil, vardenafil	↑ sildenafil	<p>Particular caution should be used when prescribing PDE5 inhibitors for the treatment of erectile 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.</p> <p><u>Use of PDE5 Inhibitors for Erectile Dysfunction</u></p> <p>Sildenafil may be used with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.</p> <p>Tadalafil may be used with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events.</p> <p>Vardenafil should not be used with PAXLOVID (see 2 CONTRAINDICATIONS).</p> <p><u>Use of PDE5 Inhibitors for Pulmonary Arterial Hypertension</u></p> <p>Coadministration of PAXLOVID and tadalafil for the treatment of pulmonary arterial hypertension is not recommended.</p>

Concomitant Drug Class: Drug Name	Effect on Concentration of 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 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.
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 K_i 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.