Paxlovid (nirmatrelvir/ritonavir)
Protease inhibitor

TOP FIVE THINGS TO KNOW ABOUT PAXLOVID AND OLDER ADULTS

1. Authorized for treatment of mild-to-moderate COVID-19 in adults aged 18 years and older with positive results of SARS-Cov-2 viral tests and at high risk of progression to severe COVID-19, including hospitalization or death. Not indicated for patients requiring hospitalization due to severe COVID-19 or as pre/post exposure prophylaxis.
2. The dose of medication is 300 mg nirmatrelvir (i.e., 2x 150mg tablets) and 100 mg ritonavir (i.e., 1 tablet) twice a day for 5 days, initiated as soon as possible after diagnosis and within 5 days of symptom onset.
3. Ritonavir is a potent inhibitor of CYP3A4 and can also inhibit other CYP450s enzymes and drug transporters. Potentially life-threatening interactions are possible. Review with a pharmacist or clinical pharmacologist is strongly recommended before prescribing.
4. For patients with moderate renal impairment (i.e., eGFR ≥30 to <60 ml/min), reduce dose to 150 mg nirmatrelvir (i.e., 1 tablet only) and 100 mg ritonavir (i.e., 1 tablet) twice daily for 5 days. Paxlovid is not recommended in patients with severe renal impairment (i.e., eGFR <30ml/min).
5. Because of a lack of data, Paxlovid is not recommended in patients with severe liver disease. No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Benefits and Risks[1] 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. Subjects were ≥18 years of age with ≥1 risk factor for progression to severe disease, including: diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were ≥60 years of age regardless of comorbidities. Subjects with COVID-19 symptom onset of ≤5 days were randomized (1:1) to 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. Individuals with a history of prior COVID-19 infection or vaccination were excluded. Delta (98%) was the predominant SARS-CoV-2 variant across both treatment arms.

In the interim analysis (n=774), Paxlovid significantly reduced the proportion of participants with COVID-19 related hospitalisation or death through Day 28 by 89.1%, compared with placebo, in participants with symptom onset ≤3 days who were at increased risk of progression to severe disease. There were no deaths in the Paxlovid group compared to 7 deaths in the placebo group. A similar proportion of participants discontinued treatment due to an adverse event with 2.4% in the Paxlovid and 4.3% in the placebo group.

The drug is authorized for mild-to-moderate COVID-19 in adults 18 years of age and older with positive SARS-Cov-2 results and at high risk of progression to severe COVID-19, including hospitalization or

death. Not authorized for treatment initiation in patients requiring hospitalization due to severe COVID-19, pre-/post-exposure prophylaxis COVID-19 and for use for greater than 5 consecutive days.

Mechanism of Action[1] Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 3C-like protease main protease (Mpro), also called 3CLpro or NSP5 protease. Inhibition of the SARS-CoV-2 3CL protease prevents it from processing polyprotein precursors, thereby hindering viral replication. Ritonavir inhibits metabolism of nirmatrelvir, allowing for therapeutic nirmatrelvir plasma concentrations.

Dose in Older Adults:[1] No dose adjustment currently recommended based on age. Product monograph states that of the total number of participants in the pivotal trial randomized to receive nirmatrelvir/ritonavir (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

300 mg nirmatrelvir (two 150 mg tablets) and 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.

Dose adjustments in renal impairment:[1]

Mild impairment: eGFR 60 to <90 ml/min - no adjustment

Moderate impairment: eGFR ≥30 to <60 ml/min- reduce dose to 150 mg nirmatrelvir (i.e., 1 tablet only) and 100 mg ritonavir twice daily for 5 days

Severe renal impairment: eGFR <30ml/min - not recommended

Dose adjustments in hepatic impairment:[1]

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 not recommended for use in patients with severe hepatic impairment.

Adverse Effects[1]

The safety of nirmaltrevir/ritonavir is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomized, placebo-controlled trial in 2,224 non-hospitalized adults aged 18 years and older with a laboratory confirmed diagnosis of SARS-CoV-2 infection and at high risk of developing severe COVID-19 illness randomized to active treatment (n=1,109) or placebo (n=1,115) twice a day for 5 days. Adverse events were reported while subjects were on study medication and through Day 34.

Adverse events (all grades regardless of causality) in the nirmaltrevir/ritonavir group (≥1%) that occurred at a greater frequency than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%). Similar proportions of

subjects discontinued treatment due to an adverse event, with 2% in the nirmaltrevir/ritonavir group and 4% in the placebo group.

Precautions:[1] Hepatic transaminase elevations, hepatitis, and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

Contraindications:[1] Patients with a history of clinically significant hypersensitivity reactions (e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to nirmatrelvir or ritonavir or any other components of the product.

Concomitant with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions, and 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 list of interactions at the end of this document).

Monitoring Parameters: Monitor patients with pre-existing liver disease for signs of worsening hepatic function. Monitor patients for symptomatic improvement and clinical deterioration. Monitoring for signs and symptoms of drug interactions will be required depending on concomitant medications.

Discontinuation/withdrawal considerations: Unlikely, as intended for 5-day treatment course only.

Pharmacodynamics:[1] 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 IC50 value of 19.2 nM. Nirmatrelvir binds directly to the SARS-CoV-2 3CL protease active site, as observed on X-ray crystallography.

Pharmacokinetics[1]

Pharmacokinetic considerations in older adults: No information available

Summary of pharmacokinetic parameters Represents data from 2 x 150 mg tablets of nirmatrelvir/ 100 mg ritonavir. Values are presented as geometric mean (geometric % CV) except median (range) for tmax and arithmetic mean ± SD for half-life.

	Nirmatrelvir	Ritonavir
AUC (µg*hr/mL)	23.01 (23)	3.60 (47)
C_{max} (µg/mL)	2.21 (33)	0.36 (46)
t_{max} (h)	3.00 (1.02-6.00)	3.98 hrs (1.48-4.20)
Half-life (h)	6.05 ± 1.79	6.1 ± 2.2
Protein binding (%)	69%	98% to 99%
Excretion	49.6% recovered in feces, 35.3% recovered in urine	86.4% recovered in feces, 11.3% recovered in urine

Effect of food: An exploratory study in 4 healthy volunteers showed that a high-fat high-calorie meal increased C_{max} and AUC 15% and 1.6%, respectively.

Metabolism: In vitro studies suggest that nirmatrelvir is primarily metabolized by CYP3A4. In plasma, only unchanged nirmatrelvir was observed. Minor oxidative metabolites were observed in the feces and urine.

Pharmacokinetics in renal impairment: Cmax and AUC of nirmatrelvir in mild renal impairment were 30% and 24% higher, in moderate renal impairment were 38% and 87% higher, and in severe renal impairment were 48% and 204% higher, respectively, compared to healthy controls.Dose adjustments needed (see dose in renal impairment)

Pharmacokinetics in hepatic impairment: Pharmacokinetics of nirmatrelvir were similar in moderate hepatic impairment compared to healthy controls. Not studied in severe hepatic impairment.

Clinically Significant Drug Interactions[1]

Pharmacokinetic:

- Ritonavir inhibits CYP3A4 and CYP2D6. Can anticipate interactions with CYP3A4 substrates (>3-fold increase in AUC) and CYP2D6 substrates (> 2-fold increase in AUC).
- Ritonavir also inhibits the activity of the following drug transporters: p-glycoprotein, breast cancer resistance protein, hepatic organic anion transporting polypeptides (OATPs) and multiantimicrobial extrusion protein 1 (MATE1).
- Ritonavir induces other cytochrome P450 enzymes (including CYP3A, CYP1A2, CYP2C9,
- CYP2C19, and CYP2B6 among others) and phase 2 metabolism, although the short treatment course likely offsets the risk of clinically significant interactions occurring.
- Nirmatrelvir and ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce therapeutic effect.
- Nirmatrelvir is not an inducer or substrate of other CYP enzymes. Based on in vitro data, nirmatrelvir may potentially inhibit P-glycoprotein and OATP1B1.

Drug Class	Drug Within Class that are Contraindicated with Paxlovid
Alpha-adrenoreceptor Antagonists	alfuzosin
Antianginal	ranolazine
Antiarrhythmics	amiodarone, bepridil[a], dronedarone, flecainide, propafenone, quinidine
Antibiotic	fusidic acid
Anticancer	apalutamide, neratinib, venetoclax
Anticoagulant	rivaroxaban
Anticonvulsant	carbamazepine, phenobarbital, phenytoin
Antifungal	voriconazole
Antigout	colchicine
Antihistamines	astemizole[a], terfenadine[a]
Antimycobacterial	rifampin
Antipsychotics	lurasidone, pimozide
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine[a], methylergonovine[a]

GI Motility Agents	cisapride[a]
Herbal Products	St. John's wort
Lipid modifying agents	lovastatin, simvastatin, lomitapide
Long-Acting Beta-adrenoceptor	salmeterol
PDE5 Inhibitors	sildenafil (*only for pulmonary hypertension),* vardenafil (*for erectile dysfunction and pulmonary hypertension)* 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. As noted above, vardenafil contraindicated.
Sedative/Hypnotics	midazolam (*oral – contraindicated, IV – can be used with dose reduction and close monitoring*), triazolam
[a] Not available in Canada	

Note that above list is note comprehensive. It only includes those drugs contraindicated with Paxlovid. Other medications for which there could be important interactions include:

- Statins: ↑ lovastatin, simavastatin, lomitapide, atorvastatin, rosuvastatin
- Steroids: ↑ fluticasone propionate, budesonide, triamcinolone, dexamethasone, prednisone
- Calcium channel blockers: ↑ diltiazem, nifedipine, verapamil, amlodipine
- Neuroleptics: possible ↑ lurasidone, perphenazine, risperidone, thioridazine, pimozide, quetiapine
- Antidepressants: possible ↑ SSRIs, venlafaxine, tricyclic antidepressants
- Antipsychotics: ↑ risperidone, quetiapine
- Anticonvulsants: possible ↑ carbamazepine, clonazepam
- Immunosuppressants: possible ↑cyclosporine, everolimus, tacrolimus
- Analgesics, narcotics: ↑ fentanyl, tramadol, propoxyphene

List serves as a guide and is not exhaustive. Consult product monograph for more information and pharmacist for full review of potential interactions, including with drugs not mentioned in monograph.

Further guidance can also be found at the Ontario COVID-19 Science Advisory Table website: Nirmatrelvir/Ritonavir (Paxlovid): What Prescribers and Pharmacists Need to Know - Ontario COVID-19 Science Advisory Table (covid19-sciencetable.ca)

Pharmacodynamic: None expected

Pharmacogenomics: No information available

References

1. Paxlovid. Product monograph. Kirkland (QC). Pfizer Canada ULC. 2022.