



Winnipeg Regional
Health Authority

Office régional de la
santé de Winnipeg

Paxlovid™

Information Session for Pharmacists

Alfred Gin, BScPharm, PharmD
Clinical Pharmacist – Infectious Diseases
Health Sciences Centre Winnipeg
WRHA Regional Pharmacy Program
June 1, 2022

Acknowledgement

The Winnipeg Regional Health Authority acknowledges that it provides health services in facilities located in Treaty One and Treaty Five territories, the homelands of the Métis Nation and the original lands of the Inuit people. The WRHA respects and acknowledges harms and mistakes, and we dedicate ourselves to collaborate in partnership with First Nation, Métis and Inuit people in the spirit of reconciliation.

Disclosures

- No conflicts to declare
- No affiliation with pharmaceutical industry

Anti-SARS-CoV-2 Treatment

- Monoclonal antibodies
- Antivirals
 - Remdesivir intravenous
 - Paxlovid™ (nirmatrelvir and ritonavir) oral
 - Initially centralized distribution models across Canada
 - Now available through participating community pharmacies in all provinces
 - Pharmacists prescribing in 4 provinces

Paxlovid™ (nirmatrelvir and ritonavir)

- Overview - Process Change
- Adverse effects
- Contraindications
- Pregnancy and breastfeeding
- Drug Interactions and Resources
- Prescriber and Pharmacist tips
- Case Examples and resource use
- Q&A

Treatment Options for COVID-19 in Manitoba

<https://sharedhealthmb.ca/covid19/treatment/>

The screenshot shows the Shared Health Manitoba website. The header includes the logo, social media icons, and a search bar. The navigation menu has tabs for COVID-19, About, Patient Care, Services, News, Careers, Contact, and Health Providers. The main content area is titled "Treatment Options for COVID-19" and includes a "Jump to paediatrics" link. The text states that treatment options are available by referral for patients meeting criteria. It lists two forms of treatment: Oral Antivirals (Paxlovid) and Remdesivir. A list of resources includes a treatment update, recommendations, a French poster, and a reminder for transplant recipients. A sidebar on the right lists various COVID-19 resources for health providers, such as operational updates, staff resources, acute care, isolation accommodations, ethics, human resources, infection control, home care, long-term care, mental health, occupational health, PPE, posters, providers, public health, return to work, specialty care, and treatment options. A "Share This Page" section at the bottom of the sidebar includes social media icons.

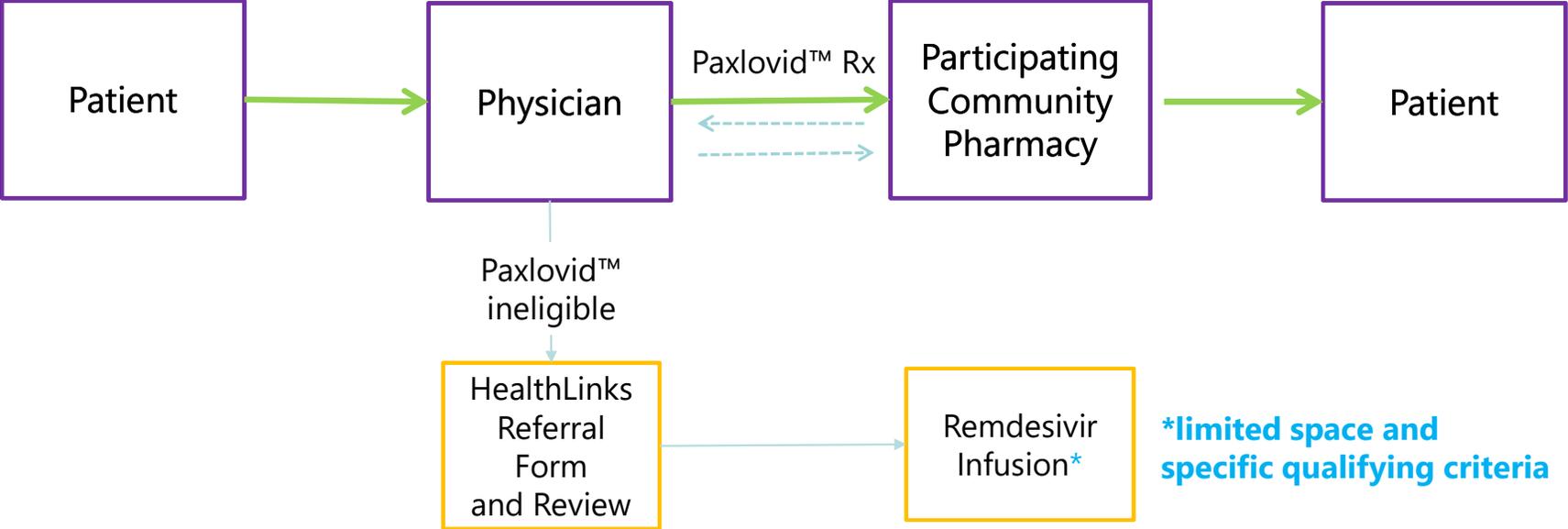
- Most up to date info always at Shared Health site
 - Documents dynamic
- Resources for physicians, prescribers, nurses, pharmacists and allied health

CARING
FOR HEALTH



Winnipeg Regional Health Authority
Office régional de la santé de Winnipeg

Expanded Paxlovid™ Access in Manitoba



Paxlovid™ in Canada

- 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.

Paxlovid™ Canadian Product Monograph. January 27, 2022

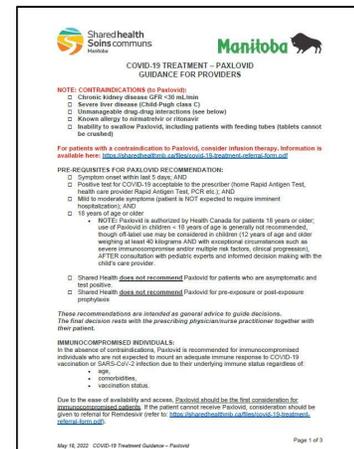
CARING
FOR HEALTH



Winnipeg Regional Health Authority
Office régional de la santé de Winnipeg

Paxlovid™ Treatment Guidance (May 18, 2022)

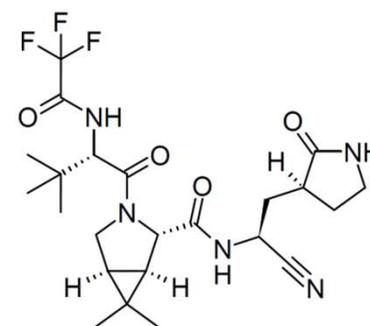
- Covid-19 symptoms within last 5 days and
 - Mild to moderate symptoms (hospitalization not imminent)
 - Test positive
- 18 yo or older
 - **Note: 12 yo or older allowed (minimum 40 kg)**
- Groups:
 - Immunocompromised unable to mount response regardless of age, comorbidities and vaccination status
 - Immunocompetent pts at risk of severe outcome (hospitalization, ICU admission, death)
 - Risk groups: age, unvaccinated/partial vaccinated, chronic health conditions, pregnancy, ethnicity

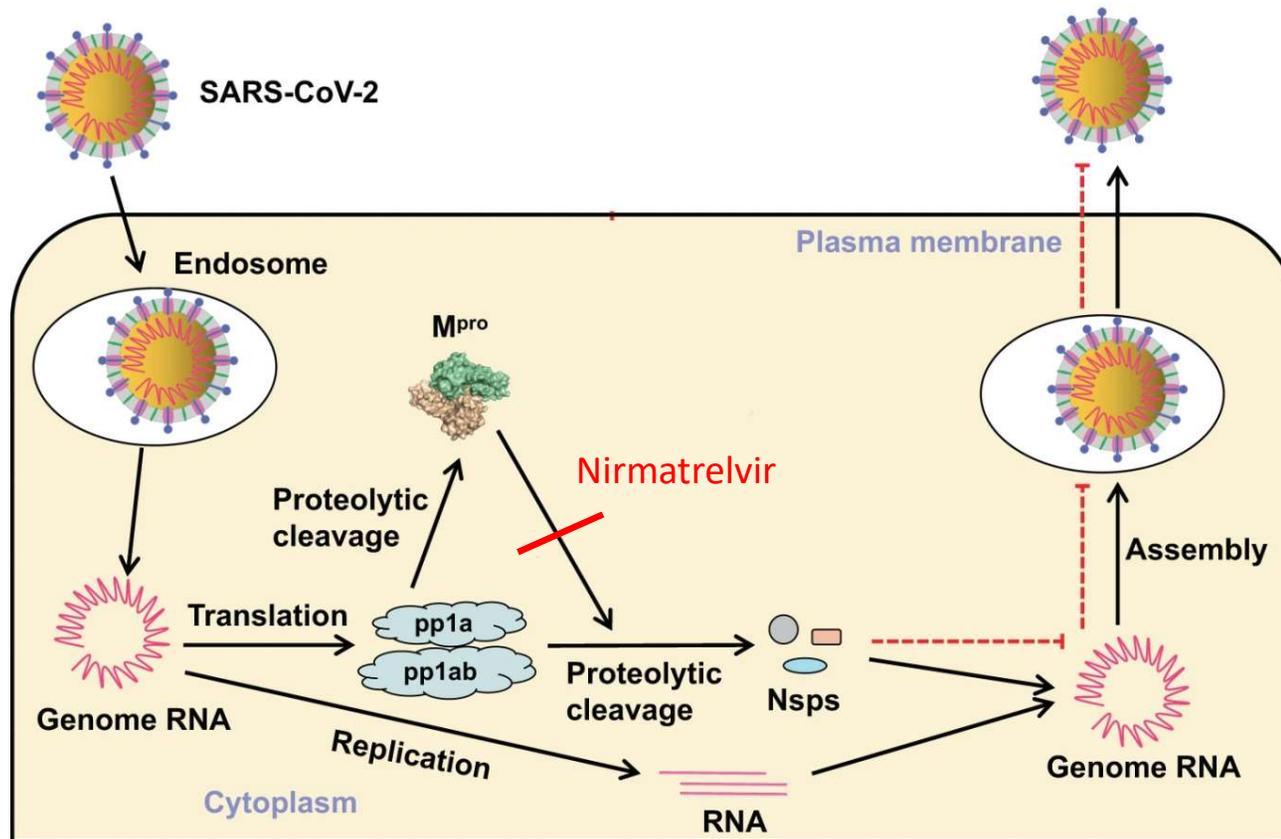


<https://sharedhealthmb.ca/files/covid-19-paxlovid-provider-guidance.pdf>

Paxlovid™ (nirmatrelvir and ritonavir)

- Nirmatrelvir
 - SARS-CoV-2 main protease (Mpro) inhibitor*
 - Primarily renally eliminated
 - Half-life doubles with eGFR <30 mL/min
 - Metabolized by CYP3A
 - Active against SARS-CoV-2 including omicron variants of concern
- Ritonavir
 - HIV protease inhibitor
 - CYP3A inhibitor used to increase (“boost”) nirmatrelvir exposure





Adapted from Mengist. Signal Transduction and Target Therapy. May 2020

Oral Nirmatrelvir for High-Risk Nonhospitalized Adults with Covid-19 (EPIC-HR)

- Nirmatrelvir and ritonavir versus placebo
- Population: non-hospitalized pts
 - >18 yo with at least 1 risk factors for severe outcome or >60 yo
 - SARS-CoV-2 lab positive
 - symptoms <5 days
- Primary endpoint: hospitalization or death any cause by Day 28

Hammond et al. NEJM. Published online Feb. 16/22 DOI: 10.1056/NEJMoa2118542

Oral Nirmatrelvir for High-Risk Nonhospitalized Adults with Covid-19 (EPIC-HR)

	Paxlovid™	Placebo
mITT combined		
Hospitalized or death all cause	8/1039 (0.8%)	66/1046 (6.3%)
88% relative risk reduction in the mITT for Paxlovid™ vs placebo (95% CI: 75%, 94%) p<0.0001		
Deaths	0	12

Hammond et al. NEJM. Published online Feb. 16/22 DOI: 10.1056/NEJMoa2118542

Paxlovid™ (nirmatrelvir and ritonavir) Adverse Events

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.

Paxlovid™ Canadian Product Monograph. January 27, 2022

Paxlovid™ Question

“I have symptoms and tested positive. I don’t have risk factors but will Paxlovid™ reduce my symptoms?”

EPIC-SR: standard risk

- Standard risk = low risk of hospitalization
- Primary endpoint: symptom reduction
 - No difference in symptoms vs placebo

Pfizer interim results: EPIC-SR (December 14, 2021)

Paxlovid™ Question 2

“I’ve been exposed to household contact who is symptomatic and rapid test positive. Can I take Paxlovid™ prophylactically?”

EPIC-PEP: post-exposure prophylaxis

- 5 vs 10 days Paxlovid™ prophylaxis in asymptomatic RAT- subject with exposure to household positive
- Primary endpoint: reduce risk of asymptomatic/symptomatic COVID-19
 - Not statistically significant vs placebo

Pfizer interim results EPIC-PEP (April 29, 2022)

What is the dosing for Paxlovid™?

- Single 5 day course (10 doses)
 - no repeat/refills, no extension.
- Dose based on eGFR*:
 - ≥ 60 mL/min
 - Nirmatrelvir 300 mg (2 tabs 150 mg) plus ritonavir 100 mg (1 tab) orally q12h
 - 30 to 59 mL/min
 - Nirmatrelvir 150 mg (1 tab) plus ritonavir 100 mg (1 tab) orally q12h

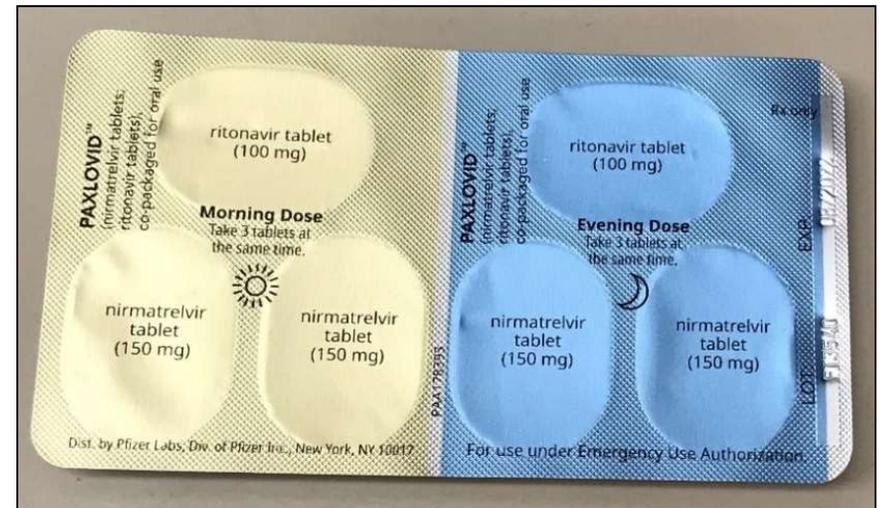
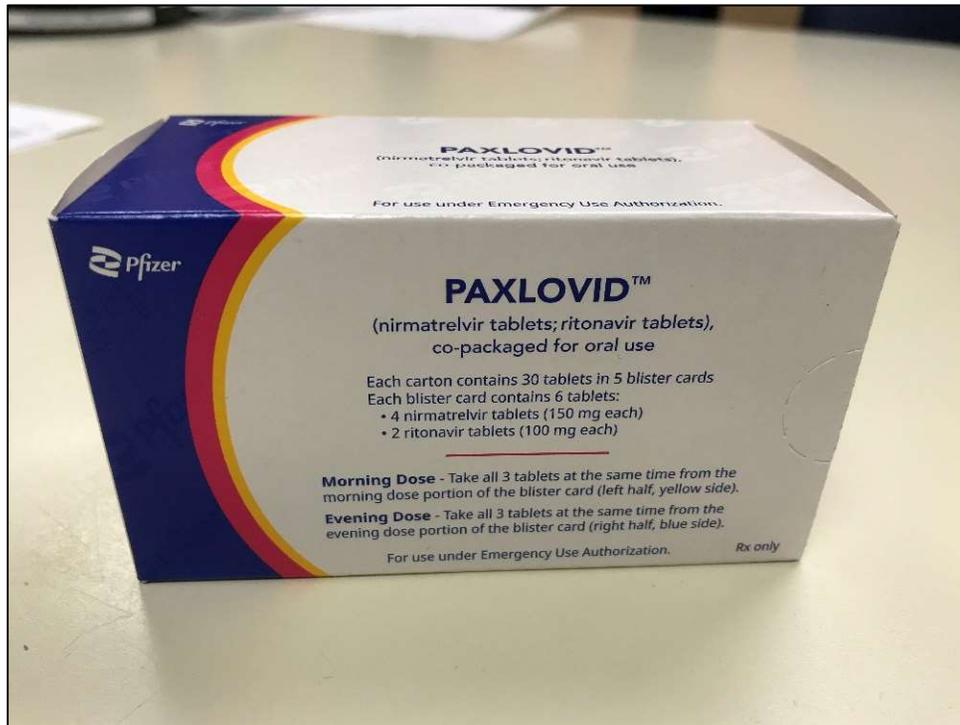
*mL/min/1.73m²

Need serum creatinine for eGFR *(Physician/Prescriber)
eGFR calculated via eChart or eGFR CKD-EPI 2021 calculators

CARING
FOR HEALTH



Winnipeg Regional Health Authority
Office régional de la santé de Winnipeg



- Box contains 5 blister cards (10 doses)
- 2 doses per card labelled Morning + Evening
- Nirmatrelvir 150 mg x 4 tabs
 - Ritonavir 100 mg x 2 tabs

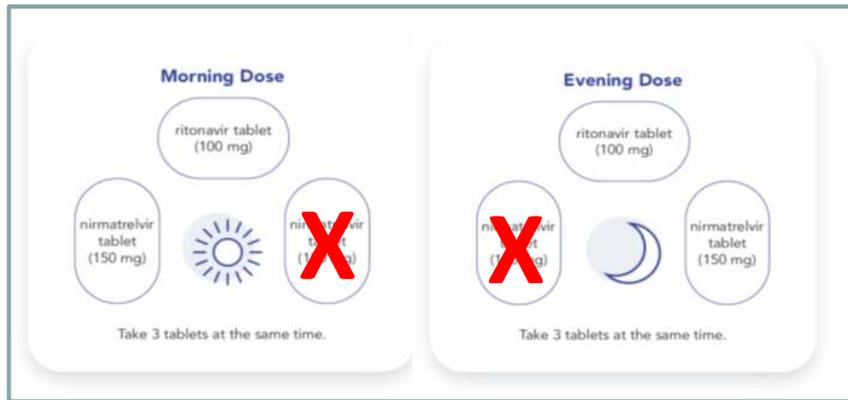
How is Paxlovid™ taken?

- Patient must be able to swallow tablet whole
 - No crushing/splitting/dissolving
 - Taken with or without food
- Missed dose
 - Take if within 8 hrs otherwise skip dose
 - Move missed dose to end of course to complete 10 doses



<https://www.nytimes.com/2022/01/19/business/covid-pill-treatment-pfizer.html>

Paxlovid™ Renal Dose* Adjustment by Pharmacy



Many Options:

- Cover empty cells with label (with or without text)
- Leave uncovered
- Other
- Let patient know what to expect re: format

*30 to 59 mL/min/1.73m²

Is Paxlovid™ contraindicated in pregnancy?

- Not contraindicated
- Clinical trial excluded pregnant women however...
 - Significant clinical and safety experience with ritonavir in pregnant women with HIV
 - Nirmatrelvir expected to be similar
- Option for Paxlovid™ should not be withheld in pt at risk
 - Discussion: benefits and clinical need may outweigh perceived risks

Paxlovid™ – Is Breastfeeding ok?

- Not contra-indicated
- Not studied in breast feeding nor in breastfed infant
 - Clinical experience with ritonavir
- Discussion with patient:
 - benefits of breast feeding and clinical need for Paxlovid™ in mother vs any potential adverse effects to infant or from underlying maternal condition
- “.....poor oral bioavailability of nirmatrelvir and small amounts of ritonavir in milk, this combination is unlikely to adversely affect the nursing infant.”*

*LactMed: <https://www.ncbi.nlm.nih.gov/books/NBK576869/>

What are the Contraindications for Paxlovid™?

- eGFR <30 mL/min
- Liver impairment – Child-Pugh class C
- Hypersensitivity to Paxlovid™
- Inability to swallow large pills
- Drug interactions
 - unmanageable drug interactions

*<https://sharedhealthmb.ca/files/covid-19-paxlovid-provider-guidance.pdf>
Paxlovid™ Canadian Product Monograph. January 27, 2022

Paxlovid™ (nirmatrelvir and ritonavir)

Drug Interactions

Ritonavir Drug Interactions

- Ritonavir is a potent irreversible inhibitor of intestinal and hepatic CYP3A
 - Onset of inhibition reaches maximal after 2 to 3 days following initiation of ritonavir
 - Offset of inhibition occurs after 3 to 5 days following discontinuation of ritonavir
- Limited data for Paxlovid™ (5 day treatment)

Paxlovid™ Drug Interactions

- Drug interaction severity range from absolute contraindication to mild depending on affected drug
- Severe drug interactions can lead to significant patient harm
- Interaction examples: Paxlovid™ and
 - atorvastatin = ↑↑ atorvastatin
 - tacrolimus = ↑↑↑↑ tacrolimus
 - rifampin = ↓↓↓↓ Paxlovid™
 - St. John's Wort = ↓↓↓↓ Paxlovid™

Unmanageable
drug interaction
Paxlovid™ ineligible

COVID-19 Treatment Update – Community Pharmacy Dispensation of Paxlovid

“As health providers with extensive knowledge regarding medications and in particular, medication interactions, pharmacists reviewing prescriptions for Paxlovid are strongly encouraged to not only flag medication interactions but also to make treatment recommendations to support prescribers where a drug interaction with Paxlovid is identified, including recommendations to hold or modify the dose of other medications, OR in the case of significant interaction, a recommendation not to proceed with Paxlovid therapy.”

MEMO

Date: May 18, 2022

To: CEOs & Leadership Teams, Manitoba Health Service Delivery Organizations
Community Pharmacists
Primary Care Providers & Clinics

From: Dr. Perry Gray, Chief Medical Officer, Shared Health
Brendon Mitchell, Regional Pharmacy Director, WRHA Pharmacy Program

Re: COVID-19 Treatment Update – Community Pharmacy Dispensation of Paxlovid

COVID-19 treatments remain an effective early measure to help prevent severe illness, particularly among those people at higher risk. To ensure both ease and equity of access to treatment, please note the following updates.

A. **Effective May 20, 2022**, participating community pharmacies will begin dispensing Paxlovid® (nirmatrelvir & ritonavir). Centralized referral for access to Paxlovid® will be discontinued. A list of participating pharmacies in communities across Manitoba will be available here: <https://www.gov.mb.ca/covid19/treatment/>.

B. To ensure equitable access to treatment, a valid Manitoba Health card/coverage will not be required by clients accessing publicly-funded Paxlovid®.

C. Centralized referral for Remdesivir remains in place. An updated referral form is available here: <https://sharedhealth.mb.ca/files/covid-19-treatment-referral-form.pdf>.

Comprehensive information regarding COVID-19 Treatment Options is available here: <https://sharedhealth.mb.ca/covid19/treatment/>. Updated guidance for providers has been developed and is now available here: <https://sharedhealth.mb.ca/files/covid-19-paxlovid-provider-guidance.pdf>.

Background Information - PAXLOVID
Indicated for the treatment of mild to moderate COVID-19 infection, Paxlovid® is an oral antiviral therapy intended for patients at high risk of progression to severe illness, including hospitalization or death.

Comprehensive information regarding Paxlovid® is available to prescribers and pharmacists.

Page 1 of 2

Shared Health, May 18, 2022

CARING
FOR HEALTH



Winnipeg Regional
Health Authority | Office régional de la
santé de Winnipeg

MEMO

Date: May 30, 2022
 To: All Medical Staff
 From: Dr. Perry Gray, Chief Medical Officer, Shared Health;
 Brendon Mitchell, Regional Pharmacy Director, WRHA Pharmacy Program

Re: Paxlovid drug-drug interactions

On the following dates, the following documents were posted on the Shared Health website as it related to prescribing of Paxlovid® in the province of Manitoba:

- [COVID-19 treatment reminder for transplant recipients](#) (May 26, 2022)
- [Treatment Update – Community Pharmacy Dispensation of Paxlovid](#) (May 18, 2022)
- [Treatment recommendations](#) (May 18, 2022)
- [Paxlovid Guidance for Providers](#) (May 18, 2022)
- [Paxlovid Drug Interactions Sheet](#) (Jan 21, 2022)
- [Paxlovid Information for Health-Care Providers](#) (Jan 21, 2022)

Treatment with Paxlovid® carries a significant risk of drug-drug interactions. Because of the propensity for a variety of different drug-drug interactions, with diverse potential outcomes, caution should be exercised when initiating therapy with Paxlovid® in patients who are taking other prescription or over-the-counter medications, herbal products or complementary/alternative medicines.

There are several resources to support pharmacists and prescribers in determining the significance of potential medication interactions:

Quick point of care references:

- Ontario Science Table Paxlovid 'need to know' – see table on page 3 & appendix: <https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-2-0/>
- BC-CDC Drug Interaction Practice Tool: http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/PracticeTool3_DrugInteractionsContraindications.pdf

More in-depth drug interaction analysis:

- Liverpool Covid-19 interaction tracker: <https://www.covid19-druginteractions.org/checker>

Where a significant drug-drug interaction precludes the use of Paxlovid®, guidance regarding alternative COVID therapeutic options can be found here: <https://sharedhealthmb.ca/files/covid-19-treatment-recommendations.pdf>

A few common drug interaction scenarios follow to illustrate how these tools can be used:

Scenario 1: Your patient is taking an anticoagulant

Rivaroxaban	C-M	↑ed levels of DOAC and ↑ bleeding risk. Can consider switch to dabigatran. *See notes
-------------	-----	---

Legend:

C-X: Contraindicated due to serious toxicity. Stopping the drug does not mitigate the interaction due to prolonged half-life, duration of enzyme induction or is not clinically appropriate due to risk or severity of condition
C-M: Co-administration is contraindicated but management strategies possible (e.g., holding drug or switch)
DDI-M: Significant interaction but management strategies possible by prescriber or with expert consultation, or monitor
OK: Interaction listed in the monograph, but the interaction has low clinical relevance

Source: BC COVID Therapeutics Committee. Drug-Drug Interactions and Contraindications

Scenario 2: Your patient is taking a calcium-channel blocker

Nifedipine	C-M	Large ↑ in nifedipine levels and cardiac clinical effects; hold if appropriate
Amlodipine	DDI-M	↑ed AUC by 2X. If BP <130, ↓ dose by 50% during treatment and restart 3 days after finishing

Source: BC COVID Therapeutics Committee. Drug-Drug Interactions and Contraindications

Scenario 3: Your patient is taking an immunosuppressant after solid organ transplant

Tacrolimus	C-M	↑ed AUCs by 10X and Cmax by 4X; consult transplant team if holding OK; TDM difficult
Cyclosporine	C-M	↑ed cyclosporine levels by 25%; narrow TI & requires TDM; consult transplant team
Sirolimus	C-M	↑ed AUCs by 10X and Cmax by 4X; consult transplant team if holding OK; TDM difficult

Source: BC COVID Therapeutics Committee. Drug-Drug Interactions and Contraindications

Scenario 4: Your patient is taking an antiplatelet agent

Drug	Recommendation	Comments
• Clozapem	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an analgesic is needed, use lorazepam, oxycodone, or tramadol at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
• Clopidogrel (Plavix)	Acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI): <ul style="list-style-type: none"> • If <1 month since ACS, use alternative COVID-19 agent. • If <3 months since ACS or <1 month since PCI (no ACS): Consider switching clopidogrel to prasugrel (if age >75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir. • If >3 months since ACS or >1 month since PCI (no ACS): Continue clopidogrel with acetylsalicylic acid (ASA) during nirmatrelvir/ritonavir therapy. If not taking ASA, consider switching to prasugrel (if age >75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir. 	Coadministration will decrease the antiplatelet effect of clopidogrel. Clopidogrel active metabolite AUC decreased by 53 to 69% when coadministered with ritonavir.

Source: Ontario Science Table. Paxlovid: What prescribers and pharmacist need to know.

Six sample scenarios

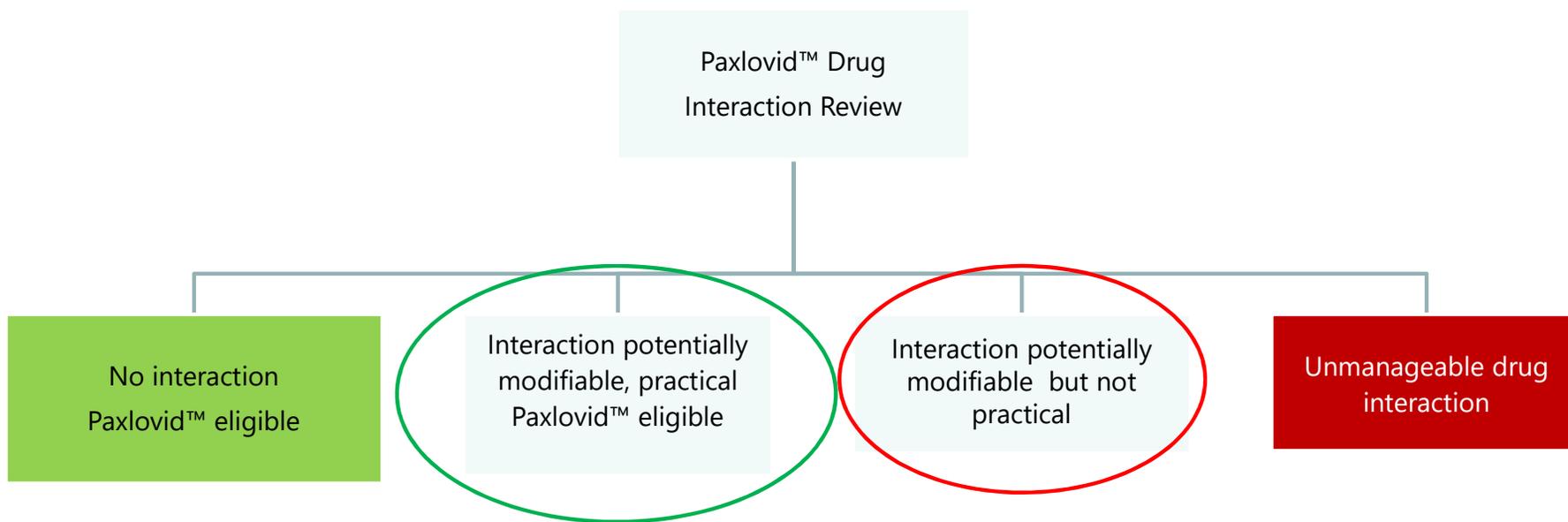
Shared Health, May 31, 2022

Scenario Examples*

- For each drug – 1 management option presented using 1 resource*
 - DOAC
 - Calcium channel blockers (nifedipine, amlodipine)
 - Antiplatelet agent (clopidogrel)
 - Statins
 - Immunosuppressants
 - Zopiclone

*note: other options may exist
that could fit a patient,
compare resources

Paxlovid™ Drug Interactions and Eligibility



Paxlovid™ Drug Interaction Management

1. Do not administer Paxlovid™
2. Hold one or more drugs
3. Modifying the dose of one or more drugs
4. Co-administering with substitute new drug



Shared health
Soins communs
Manitoba



Manitoba

Potentially clinically significant drug interactions with nirmatrelvir-ritonavir (PAXLOVID®)

1. Medications which should not be used in combination with nirmatrelvir-ritonavir where other therapies may be preferred:

Even if a patient's medications are discontinued at the point of care, nirmatrelvir-ritonavir interactions may be particularly problematic and alternative therapies should be considered. Some of the reasons for this may include: long half-life of the interacting medication, making discontinuation of the medication an ineffective strategy in an appropriate timeframe, induction of enzymes which may diminish the effectiveness of nirmatrelvir-ritonavir, high risk for significant morbidity if combined with nirmatrelvir-ritonavir.

<ul style="list-style-type: none"> Afluzosin Amiodarone Apalutamide Bosentan Cabozantinib Carbamazepine Cisapride Clozapine Cobimetinib Colchicine Dabrafenib Disopyramide Domperidone Dronedronone Eltasvir-grazoprevir Enzalutamide Erdafitinib Ergot derivatives (e.g. dihydroergotamine, ergonovine) Fentanyl¹ Flecainide Garlic (supplement) Gefitinib Glecaprevir-pibrentasvir Infigratinib Isavuconazole (isavuconazonium sulfate) Ivabradine Lamotrigine Lorlatinib Lumacaftor 	<ul style="list-style-type: none"> Lurasidone Macitentan Mexiletine Mitotane Neratinib Pazopanib Phenobarbital Phenytoin Pimozide Prasertinib Primidone Propafenone Quinine Quinidine Quinine Rameltecsine Rifabutin Rifampin Ritapentine Sofosbuvir-velpatasvir-voxilaprevir Sildenafil² St. John's Wort Tadalafil² Tepotinib Ticagrelor Tolvaptan Valproic acid and derivatives (including divalproex) Vardenafil² Venetoclax Vorapaxar
--	--

¹ Applies to transdermal formulations (e.g. patches), as well as to illicit use, in-hospital use, or use closely monitored by a healthcare provider to be evaluated on a case-by-case basis

² When used for pulmonary hypertension or benign prostatic hyperplasia.

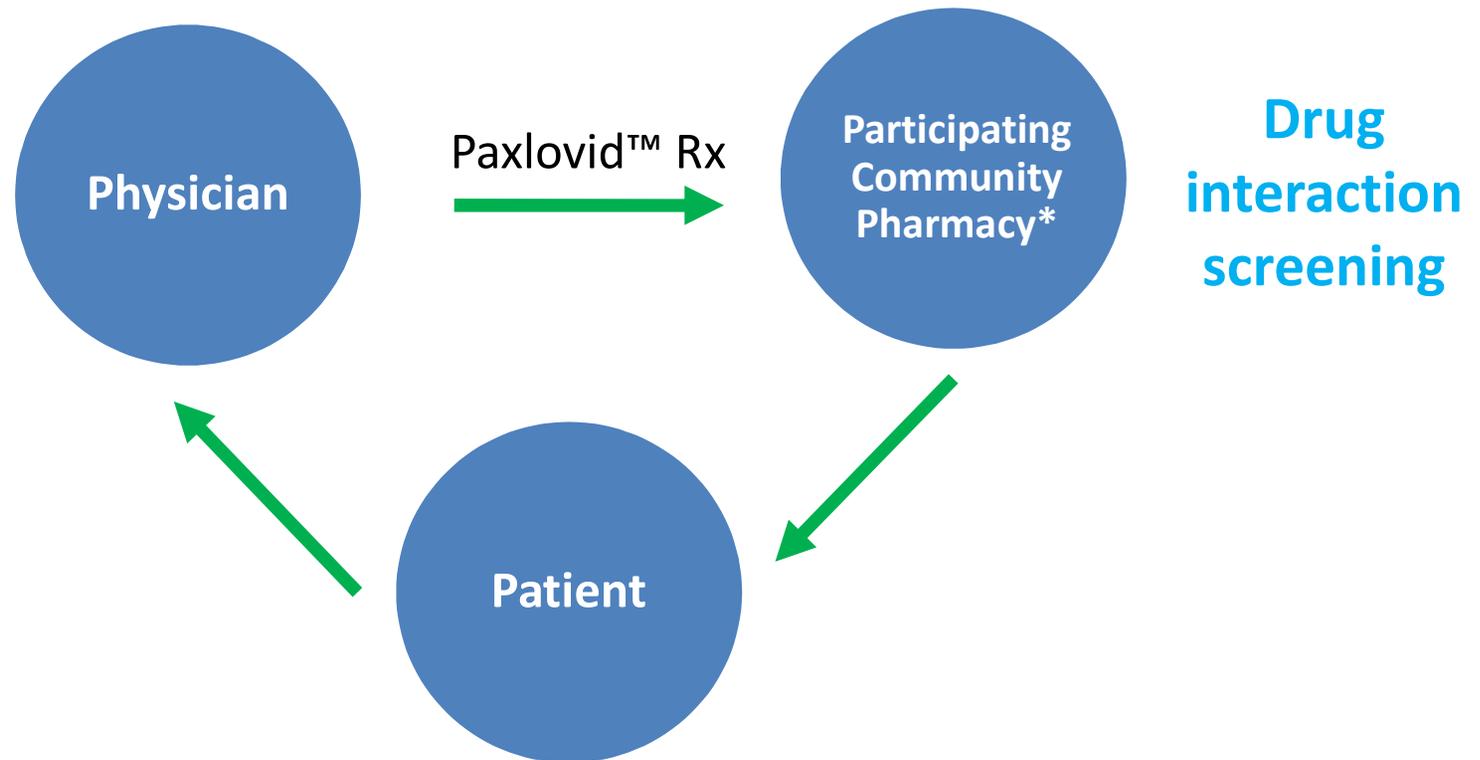
Jan. 21, 2022
Potentially clinically significant drug interactions with PAXLOVID® v4.0
1

*<https://sharedhealthmb.ca/files/covid-19-paxlovid-drug-interactions.pdf>

Drug Interaction Management Considerations

- Consider practicality
 - Number of drugs affected and potential changes
 - Ability of patient
 - 45 yo vs 91 yo
 - Family/caregiver assistance?
 - Written instructions?
 - Patient's bubble/blister packs for meds?

Paxlovid™ flow



*<https://gov.mb.ca/covid19/treatment/paxlovid-locations.html>

Pharmacist Paxlovid™ Drug Interaction Screening

- Review DPIN for medications
- Medication review with patient
 - Correlate with DPIN: new changes/stop
 - Non-prescription medications and recreational products
 - Herbal products e.g. St. John's Wort
- Identify drug interactions and management options
- Recommend management options to prescriber including “not eligible for Paxlovid™” due to unmanageable drug interaction

Drug Interaction Resources

<u>Resource Examples</u>	<u>Type</u>	<u>URL</u>
Shared Health Covid-19 Treatment Options	Documents Videos Links	https://sharedhealthmb.ca/covid19/treatment/
Liverpool Covid-19 Interaction Checker	Online search Phone App Document	https://www.covid19-druginteractions.org/checker
Ontario Science Table: Paxlovid™ Need to Know	Documents	https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-2-0/
BC-CDC Drug Interactions and Contraindications	Documents Videos	http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/PracticeTool3_DrugInteractionsContraindications.pdf

University of Liverpool Covid-19 Drug Interaction Checker

 COVID-19 Drug Interactions 

About Interaction Checkers Prescribing Resources Contact Us

Interactions with selected WHO Essential Medicines and Paxlovid (nirmatrelvir/ritonavir) now available in the Prescribing Resources section – [click here for the PDF](#)

If a drug is not listed below it cannot automatically be assumed it is safe to coadminister.

COVID Drugs	Co-medications	Drug Interactions
<input type="text" value="nirma"/>	<input type="text" value="alfu"/>	<input type="checkbox"/> Check COVID/COVID drug interactions
A-Z Class Trade	A-Z Class	Reset Checker
<input checked="" type="checkbox"/> Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]	<input checked="" type="checkbox"/> Alfuzosin	Switch to table view Results Key
<input checked="" type="checkbox"/> Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]	<input checked="" type="checkbox"/> Alfuzosin	Do Not Coadminister
		Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]
		Alfuzosin
		More info
		Quality of Evidence: Very Low
		Summary: Coadministration with alfuzosin with potent CYP3A4 inhibitors, such as ritonavir, is contraindicated. Coadministration may increase alfuzosin concentrations due to

 COVID-19 Drug Interactions 

About Interaction Checkers Prescribing Resources Contact Us

Interactions with selected WHO Essential Medicines and Paxlovid (nirmatrelvir/ritonavir) now available in the Prescribing Resources section – [click here for the PDF](#)

If a drug is not listed below it cannot automatically be assumed it is safe to coadminister.

COVID Drugs	Co-medications	Drug Interactions
<input type="text" value="nirma"/>	<input type="text" value="alfu"/>	<input type="checkbox"/> Check COVID/COVID drug interactions
A-Z Class Trade	A-Z Class	Reset Checker
<input checked="" type="checkbox"/> Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]	<input checked="" type="checkbox"/> Alfuzosin	Switch to table view Results Key
<input checked="" type="checkbox"/> Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]	<input checked="" type="checkbox"/> Alfuzosin	Do Not Coadminister
		Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]
		Alfuzosin
		More info
		Quality of Evidence: Very Low
		Summary: Coadministration with alfuzosin with potent CYP3A4 inhibitors, such as ritonavir, is contraindicated. Coadministration may increase alfuzosin concentrations due to

University of Liverpool

Liverpool Drug Interactions Group



Interactions with Essential Medicines & Nirmatrelvir/ritonavir (NMV/r)

Charts produced 8 March 2022

Page 2 of 2

Please check www.covid19-druginteractions.org for updates.

Legend

Colour/Symbol	Recommendation for NMV/r use
! Do not co-administer	Do not use NMV/r ⇒ alternative COVID-19 therapy Risk of serious toxicity. Stopping the drug does not mitigate the interaction due to its prolonged half-life.
✗ Do not co-administer	Do not use NMV/r ⇒ alternative COVID-19 therapy Strong inducer can jeopardize NMV/r efficacy due to persisting induction after stopping the drug.
Do not co-administer	NMV/r use ONLY possible if drug is paused or replaced by a non-interacting drug Risk of serious toxicity. Only start NMV/r if the drug can be safely paused or replaced. Drug can be resumed 3 days after completing NMV/r therapy.
□ Potential interaction Dose adjustment and/or close monitoring required.	Stop or replace drug if possible or consult specialist for dose adjustment/monitoring to allow use with NMV/r Ideally, only start NMV/r if the drug can be safely paused or replaced. Alternatively, dose adjust/monitor. Refer to www.covid19-druginteractions.org for detailed information.
Potential interaction Manageable by counselling patient	Proceed with NMV/r Interaction manageable by counselling the patient about potential interaction and advising to temporarily stop the drug if feeling unwell.
Weak interaction No action needed	Proceed with NMV/r Drug metabolized partially by CYP3A4 or with low risk of adverse event from interaction.
No interaction expected	Proceed with NMV/r

The PDF chart contains multiple tables listing drug classes and their interactions with NMV/r. Key categories include:

- ACE inhibitors:** Lisinopril, Enalapril, Ramipril, etc.
- Anticoagulants:** Warfarin, DOACs (Dabigatran, Rivaroxaban, Apixiban), Heparin, etc.
- Antidepressants:** SSRIs (Citalopram, Escitalopram, Sertraline, etc.), SNRIs (Venlafaxine, Desvenlafaxine), Tricyclics (Amitriptyline, etc.), MAOIs (Moclobemide, etc.).
- Antipsychotics:** Haloperidol, Risperidone, etc.
- Cardiovascular drugs:** Beta-blockers, Calcium channel blockers, Diuretics, etc.
- Diabetes medications:** Insulin, Sulfonylureas, etc.
- Drugs of Abuse:** Alcohol, Cocaine, etc.
- Enzyme Inducers/Inhibitors:** Carbamazepine, Phenytoin, Rifampin, etc.
- Herbal products:** St. John's Wort, Ginseng, etc.
- Other:** Antacids, PPIs, SGLT2 inhibitors, etc.

PDF chart

https://covid19-druginteractions.org/prescribing_resources/paxlovid-essential-medicines



Winnipeg Regional Health Authority
Office régional de la santé de Winnipeg

Ontario Science Table

Nirmatrelvir/Ritonavir (*Paxlovid*) Drug Interactions:

This is not an exhaustive list. Consultation with a pharmacist who can obtain a complete medication, recreational, and natural health product history from the patient is recommended prior to prescribing nirmatrelvir/ritonavir.

Symbol	Severity	Recommendation	Rationale
	Contraindicated	Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.	Stopping the drug will not mitigate the interaction (e.g., prolonged half-life, narrow therapeutic index, prolonged enzyme-inducing effects which may decrease effectiveness of nirmatrelvir/ritonavir). Do not coadminister due to risk of serious toxicity.
	Contraindicated (use within past 14 days)		
	Do not coadminister	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Significant ↑ in drug concentrations expected. Do not coadminister due to risk of serious toxicity.
	Caution	Therapy modification required (see Appendix).	Significant ↑/↓ in drug concentrations expected, which may lead to serious toxicity or impaired efficacy. Only coadminister if the interacting drug can be safely held or dose-adjusted and closely monitored (see Appendix). Expert consultation may be useful.
	Drug interaction not likely to be clinically relevant	Continue with standard dosing.	Although mentioned in the monograph, clinically relevant interaction is not anticipated (e.g., minimal impact on certain metabolic pathways, wide therapeutic index, and short course of nirmatrelvir/ritonavir).

<https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-2-0/>

BC Covid Therapeutics Committee

Legend:

CI-X: Contraindicated due to serious toxicity. Stopping the drug does not mitigate the interaction due to prolonged half-life, duration of enzyme induction or is not clinically appropriate due to risk or severity of condition

CI-M: Co-administration is contraindicated but management strategies possible (e.g., holding drug or switch)

DDI-M: Significant interaction but management strategies possible by prescriber or with expert consultation, or monitor

OK: Interaction listed in the monograph, but the interaction has low clinical relevance

TI: Therapeutic Index; **T_{1/2}:** Half-life; **AUC:** Area Under Curve (cumulative drug exposure); **↑:** Increase; **↓:** Decrease

Drug	Drug Interaction Type, Information and Management Strategy	
Abemaciclib	DDI-M	Oral anticancer agent. ↑'ed abemaciclib levels. Dose ↓ to 100mg BID w/ BCCA consultation
Alfuzosin	CI-M	↑↑ hypotension. If appropriate, hold drug; restart 3 days after finishing treatment
Almotriptan	DDI-M	↑↑'ed levels. For migraines, use 6.25mg max dose, up to 12.5mg/24h period
Alprazolam	DDI-M	↑↑'ed AUC by 2-5X. If appropriate, hold drug or significantly ↓ dose

http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/PracticeTool3_DrugInteractionsContraindications.pdf

Paxlovid™ Screening

common drugs encountered and management options

- Statins
 - Hold for 8 days total: Paxlovid™ (5 days) and for another 3 days after
- DOACs (e.g. apixaban, rivaroxaban)
 - different options
- Amlodipine
 - decrease dose 50% for 8 days or hold if low dose
- Zopiclone
 - reduce dose or hold
- Tacrolimus

Paxlovid™ Screening Case #1

57 yo with crohn's – DPIN and Pt Med History

- Infliximab last dose 2 weeks ago
- Alfuzosin 10 mg daily
- Atorvastatin 20 mg daily
- Vitamin D, multi-vitamin, Tums® PRN

Comparison of Paxlovid™ Drug Interaction Resources*

Alfuzosin

	Liverpool	Ontario Science Table	BC-CDC
Interaction	Do Not Co-administer 	Do Not Coadminister 	CI-M 
Pharmacokinetic rationale	Yes	Yes	Yes
Management	Hold during Paxlovid and restart after 3 days after last dose	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	↑↑ hypotension. If appropriate, hold drug; restart 3 days after finishing treatment

*refer to resource for full details

Comparison of Paxlovid™ Drug Interaction Resources Atorvastatin

	Liverpool	Ontario Science Table	BC-CDC
Interaction	Potential Interaction 	Caution 	DDI-M 
Pharmacokinetic rationale	Yes	Yes	Yes
Management	Hold during Paxlovid and restart after 3 days after last dose OR Decrease atorvastatin to 10 mg daily while on Paxlovid	Hold during Paxlovid restart after 2 days after last dose OR Decrease atorvastatin to 10 mg daily while on Paxlovid	↑'ed levels. Hold atorvastatin during treatment and restart 3 days after finishing

*refer to resource for full details

Paxlovid™ Screening Case #1

57 yo with crohn's – DPIN and Pt Med History

- Infliximab last dose 2 weeks ago
- Alfuzosin 10 mg daily
- Atorvastatin 20 mg daily
- Vitamin D, multi-vitamin, Tums® PRN

Recommendation to prescriber and counselling to patient (when approved):

- a) Hold alfuzosin for 8 days while on Paxlovid (5 days and for another 3 days after)
- b) Hold atorvastatin for 8 days while on Paxlovid (5 days and another 3 days after)

Paxlovid™ Screening Case #1A

57 yo with crohn's – DPIN and Pt Med History

- Infliximab last dose 2 weeks ago
- Alfuzosin 10 mg daily
- Atorvastatin 20 mg daily
- Amiodarone
- Vitamin D, multi-vitamin, Tums® PRN

Comparison of Paxlovid™ Drug Interaction Resources*

Amiodarone

	Liverpool	Ontario Science Table	BC-CDC
Interaction	Do Not Co-administer 	Contraindicated 	CI-M 
Pharmacokinetic rationale	Yes	Yes	Yes
Management	Amiodarone has a long elimination half-life and the risk of drug-drug interactions may not be overcome even by stopping amiodarone administration. Consider an alternative COVID-19 treatment.	Do not use nirmatrelvir/ritonavir	↑↑'ed amiodarone levels. Prolonged T1/2 and narrow TI; could consider hold w/ consultation

*refer to resource for full details

Paxlovid™ Screening Case #1A

57 yo with crohn's – DPIN and Pt Med History

- Infliximab last dose 2 weeks ago
- Alfuzosin 10 mg daily
- Atorvastatin 20 mg daily
- Amiodarone
- Vitamin D, multi-vitamin, Tums® PRN

Recommendation to prescriber

- Patient not eligible for Paxlovid™ due unmanageable drug interaction between Paxlovid™ and the long half-life of amiodarone. Consider alternative treatment.

Paxlovid™ Screening Case #2

49 yo renal transplant - DPIN and Pt Med History

- Tacrolimus
-
-
-
-
-
-
-
-

Paxlovid™ Ineligible

Comparison of Paxlovid™ Drug Interaction Resources*

Tacrolimus

	Liverpool	Ontario Science Table	BC-CDC
Interaction	Do Not Co-Administer 	Do not coadminister 	CI-M 
Pharmacokinetic rationale	Yes	Yes	Yes
Management	Consider alternative treatment; Possible options require very close monitoring.	Do not coadminister. TDM difficult.	Increased AUCs by 10X and Cmax 4X; consult transplant team if holding OK; TDM difficult

We would not attempt to TDM the interaction

*refer to resource for full details

Transplant Population and Paxlovid™ in Manitoba?




MEMO

Date: May 26, 2022

To: CEOs & Leadership Teams, Manitoba Health Service Delivery Organizations
Community Pharmacists
Access Centres and Health Links-Info Santé
Primary Care Providers & Clinics

From: Dr. Julie Ho, Medical Director, Transplant Manitoba Adult Kidney Program

Re: COVID-19 Treatment Reminder for Transplant Recipients

COVID-19 treatments remain an effective early measure to help prevent severe illness, particularly among those people at higher risk.

For solid organ transplant recipients with COVID-19, Transplant Manitoba recommends **avoiding Paxlovid**, and instead choosing alternatives such as remdesivir.

Prescribers/Pharmacists NOTE: Ritonavir is known to have significant drug-drug interactions, including a strong inhibition of CYP3A4. The use of nirmatrelvir/ritonavir with patients who are on cyclosporine, tacrolimus or sirolimus leads to a significant rise in drug concentrations and can cause serious adverse outcomes.

If you have questions or concerns, OR if you think your solid organ transplant recipient patient may be eligible to receive Paxlovid, please contact the appropriate transplant clinic physician, identified below:

- Kidney - (204) 787-3138
- Liver - (204) 787-5137
- Lung - (204) 787-3138
- Heart - (204) 258-1296 or (204) 258-1077
- Pediatrics – page the appropriate prescriber through HSC paging (204) 787-2071.

Centralized referral for Remdesivir remains in place. An updated referral form is available here: <https://sharedhealthmb.ca/files/covid-19-treatment-referral-form.pdf>

	Paxlovid™ Effect	Recommendation
Tacrolimus	↑↑↑↑	<p>Avoid Paxlovid™ Consider remdesivir. Contact Transplant Program if needed</p>
Sirolimus	↑↑↑↑	
Cyclosporine	↑↑↑↑	

Shared Health May 26, 2022

Paxlovid™ Screening Case #3

42 yo with acute coronary syndrome and stent insertion, asthma

- Apixiban
- Metformin
- Salbutamol inhaler
- Breo Ellipta inhaler
- Multi-vitamin

Comparison of Paxlovid™ Drug Interaction Resources**

Apixiban

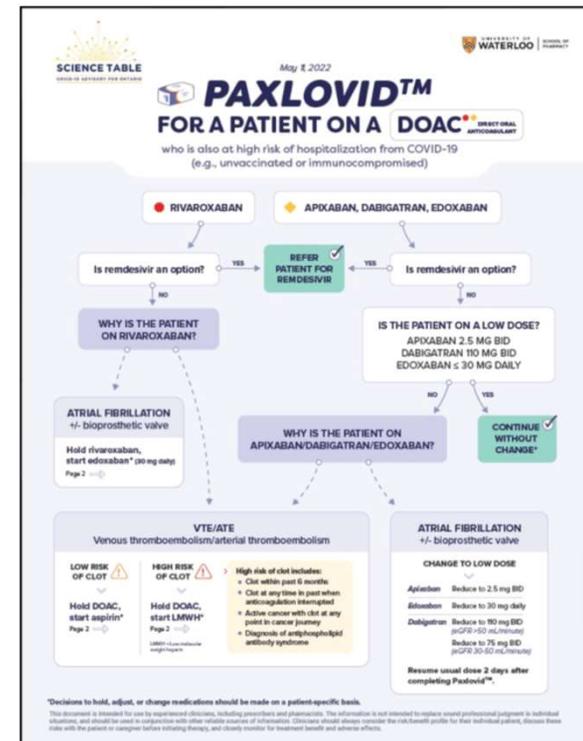
	Liverpool	Ontario Science Table	BC-CDC
Interaction	Do Not Co-Administer 	Do not coadminister 	CI-M 
Pharmacokinetic rationale	Yes	Yes	Yes
Management	Many options depends on indication A. Fib vs VTE Hold, dose reduce or use alternative VTE consider switching to LMWH or low dose aspirin**	Many options depends on indication A. Fib vs VTE Hold, dose reduce or use alternative VTE consider switching to LMWH or low dose aspirin See Paxlovid and DOAC document	↑'ed levels of apixaban leading to ↑ bleeding. Can consider switch to dabigatran. *See notes

**refer to resource for full details

Paxlovid™ and DOACs

Ontario Science Table

- DOAC type?
- Indication?
 - AFib vs VTE; artificial valve
- Dose?
- Options:
 - continue/hold/dose change/alternate agent/ or avoid Paxlovid™

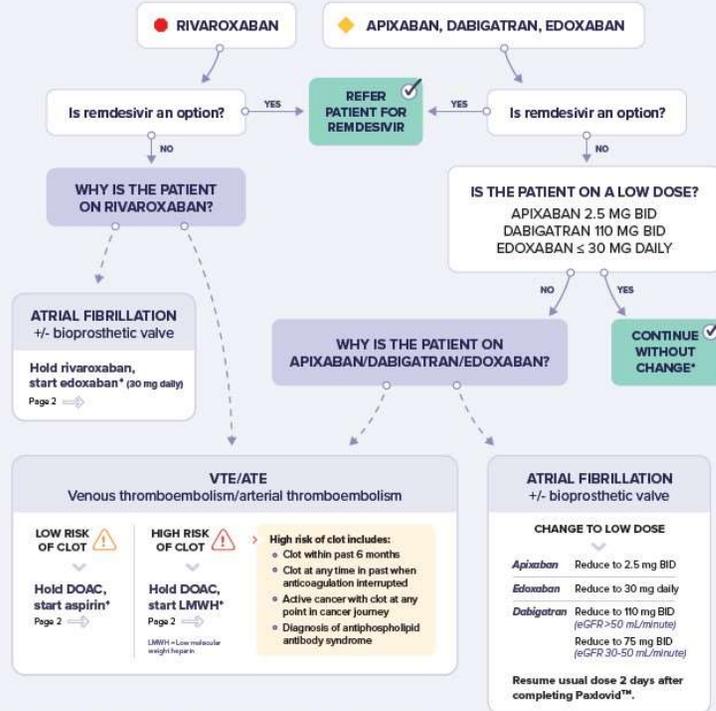


<https://covid19-sciencetable.ca/sciencebrief/paxlovid-for-a-patient-on-a-doac/>

PAXLOVID™ FOR A PATIENT ON A DOAC*

DIRECT ORAL ANTICOAGULANT

who is also at high risk of hospitalization from COVID-19
(e.g., unvaccinated or immunocompromised)

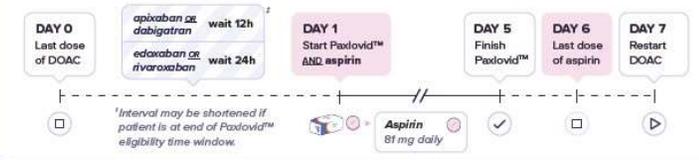


*Decisions to hold, adjust, or change medications should be made on a patient-specific basis.

This document is intended for use by experienced clinicians, including prescribers and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Clinicians should always consider the risk/benefit profile for their individual patient, discuss these risks with the patient or caregiver before initiating therapy, and closely monitor for treatment benefits and adverse effects.

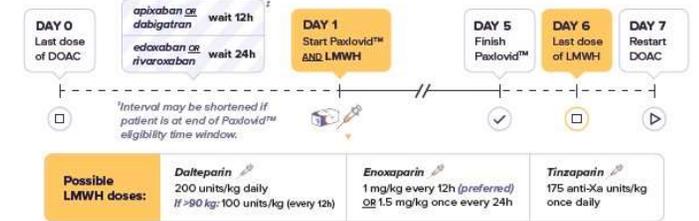
How to hold a DOAC and start aspirin:

VTE/ATE: **LOW RISK OF CLOT**



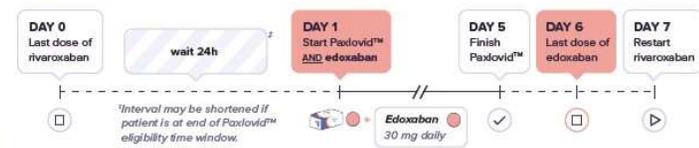
How to hold a DOAC and start LMWH:

VTE/ATE: **HIGH RISK OF CLOT**



How to hold rivaroxaban and start edoxaban:

ATRIAL FIBRILLATION



◆ People who take a DOAC should stay up to date with their COVID-19 vaccines, including boosters.

It can be challenging to manage drug interactions between COVID-19 treatments and DOACs. Vaccination can reduce the risk of needing treatment for COVID-19.

Contributors: Kelly Grindrod, BScPharm, PharmD, MSc, Claudia Bucco, BScPharm, PharmD, ACPR, Stephanie Carlin, PharmD, ACPR, Andrea Christie, MD, CCFP, Noah Ivers, MD, PhD, CCFP, Heather Kerland, PharmD, FCSHP, Tara Khan, MD, MSc, CCFP, FCFP, Kari LeBlanc, BScPharm, PharmD, ACPR, Catalina Mazzolin, PharmD, PhD, Kate Miller, MD, CCFP, FCFP, Mercedes Pang, Assoc. MD, FRCPC, Adrian Poon, BA, Alice Tsang, PharmD, FCSHP, AA-HVP, Kristen Watt, BScPharm, RPh, Samira Jeejee, MD, PhD, FRCPC. Reviewed by: Rosemary Kileen, BScPharm, PGCert, RPh.

For questions about the reproduction, adaptation, translation, or other uses of this material, contact: phrep@uwaterloo.ca

Financial contribution from:

Public Health Agency of Canada



Paxlovid™ and DOACs

BC-CDC (BC specific)

- Consider switch dabigatran x 10 days
- If pt can follow instructions; can fill dabigatran Rx, and amendable to follow-up call from pharmacist
- Dabigatran dose adjusted based on eGFR

DOACs: Rivaroxaban and Apixaban: STEP BY STEP INSTRUCTIONS

Rivaroxaban and Apixaban are two of the most common drugs that are contraindicated with nirmatrelvir/ritonavir. Due to the number of patients on these drugs, the severity of the condition and the fact that COVID-19 is a hypercoagulable state, thrombosis specialists have recommended a 10-day switch to dabigatran in *select patients*. Please see notes below pertaining to patients with Cancer-associated Thrombosis (CAT).

The switch should only be attempted for patients who can follow clear directions, who can fill the dabigatran prescription and who will be amenable to follow-up by a pharmacist by phone. Provide clear counselling AND have the patient repeat the directions back. Ensure patient understands that they will NOT take dabigatran with their current DOAC at the same time. Describe/show them the tablets they are to hold.

TO PRESCRIBE:

1. Give the patient a new prescription for the dabigatran, dosed according to their eGFR/age for 10 days.
2. State to hold rivaroxaban or apixaban for the 10 days on the dabigatran prescription.
3. Specify on the Paxlovid prescription that this change is being implemented. The pharmacist dispensing Paxlovid will phone the patient to follow-up to ensure the directions are being followed. The pharmacy involved in the Paxlovid prescription may be a different pharmacy processing the dabigatran, hence document on both prescriptions.
4. Fill out Special Authority using eForm. Select "Other" as the reason and choose Paxlovid DDI. If you are not set up for eForm, call Pharmacare directly and apply for SA over the phone. Do not fax the form as it will not be processed in a timely manner. See Appendix.
5. If you have doubts that the patient will not follow these directions, do not prescribe Paxlovid

If eGFR or renal function available:

eGFR \geq 50	dabigatran 150 mg BID.
eGFR 30-49	dabigatran 110 mg BID.
eGFR <30	do not use dabigatran.

If eGFR or renal function unknown:

age < 75	dabigatran 150 mg BID.
age \geq 75	dabigatran 110 mg BID.

1. Start first dose when patient would normally take next dose of rivaroxaban or apixaban.
2. If patient already on reduced dose rivaroxaban (10 or 15 mg once daily) or apixaban (2.5 mg twice daily), switch to dabigatran 110 mg BID.
3. DO NOT take with ASA, NSAIDs or other anticoagulants.

For full details see http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/PracticeTool3_DrugInteractionsContraindications.pdf

CARING
FOR HEALTH



Winnipeg Regional
Health Authority Office régional de la
santé de Winnipeg

Paxlovid™ Screening Case #3

42 yo with history acute coronary syndrome and stent insertion, asthma

- Apixiban
- Metformin
- Salbutamol inhaler
- Breo Ellipta inhaler
- Multi-vitamin

Example:

Conversation with prescriber re: options and indication
Recommendation(s) and counselling to patient (when approved):

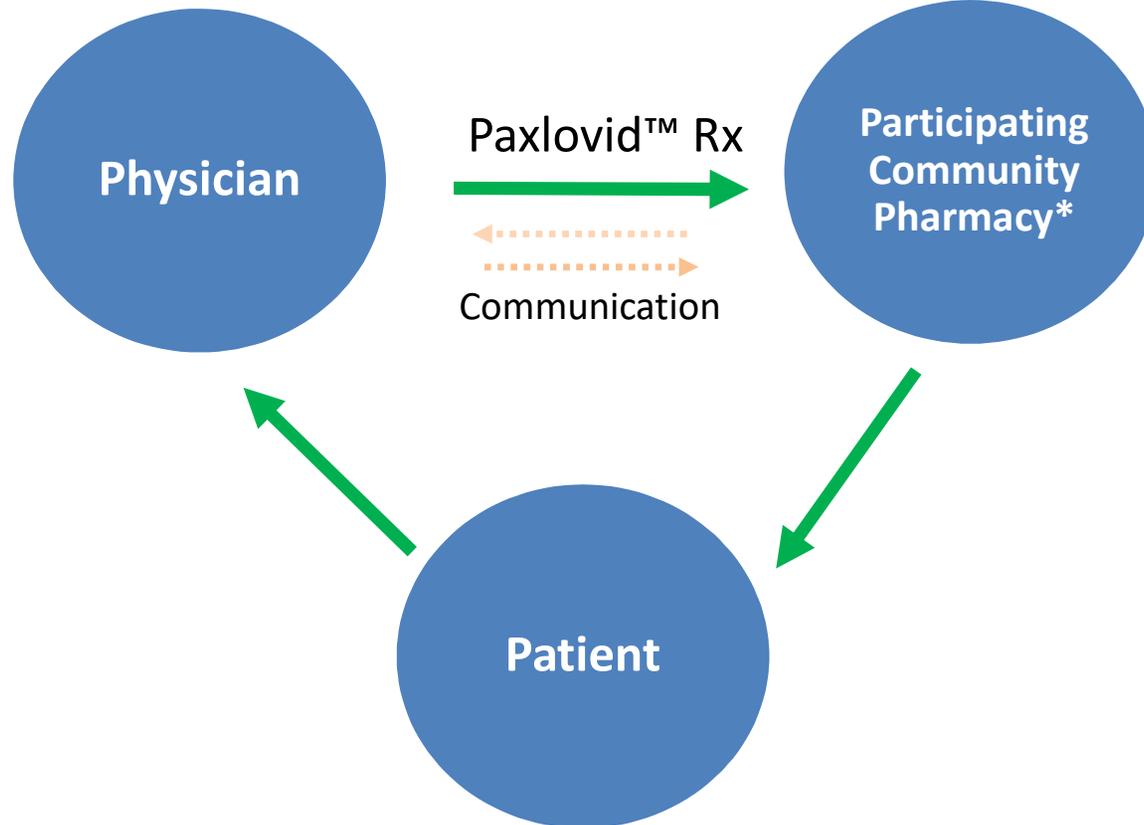
- a) Low risk VTE: consider low dose aspirin in place of apixaban for 7-8 days while on Paxlovid (5 days) and 2-3 days after
- b) High risk VTE: consider LMWH e.g. dalteparin subcut in place of apixaban for 7-8 days while on Paxlovid (5 days) and 2-3 days after

Drug Interaction Keypoints

- Resources generally in agreement but differences do occur
- Resources are not exhaustive
- Drugs not listed in the drug interaction resources DOES NOT mean 'no interaction'
 - Drug not added or overlooked
 - New drug or combination drug
 - Monograph list 'other' CYP3A inhibitors but not ritonavir
 - Pharmacists may need to investigate further

Paxlovid™ flow

- **Clinical appropriateness**
- **Initial screen** including drug interactions



- **Drug interaction screening**
- Provide recommendations to MD if applicable including 'not to use Paxlovid™'

*<https://gov.mb.ca/covid19/treatment/paxlovid-locations.html>

Paxlovid Screening Case #4

73 yo rheumatoid arthritis – DPIN and Pt Med Hx
competent knowledgeable patient

- Adalimumab weekly subcut
- Methotrexate twice weekly subcut
- Folic acid
- Duloxetine 90 mg daily
- Celecoxib 200 mg daily
- Esomeprazole 80-120 mg daily
- Gabapentine 300 mg TID
- Prednisone 5 mg daily
- Diclofenac 8% topical compounded
- OxyNeo 40 mg BID-TID
- Percocet 4-12 /day depending on pain
- Trazodone 200 mg HS

Paxlovid™ Screening Case #4 Assessment

	Interaction*	Recommendation	Comment
OxyNeo and Percocet	<ul style="list-style-type: none"> Potential interaction, weak evidence Potential increased oxycodone, consider dose reduction 	Decrease OxyNeo to 40 mg BID for 8 days total (while on Paxlovid (5 days) and 3 days after)	<p>Patient to titrate pain control with Percocet; adjust OxyNeo if needed;</p> <p>Goal: Maintain pain control</p>
Trazodone	<ul style="list-style-type: none"> Trazodone metabolized by CYP3A Potential increased trazodone concentrations 	Decrease to 100 mg for 8 days total (while Paxlovid (5 days) and another 3 days after)	<p>Discussed with patient and recommendation forwarded to prescriber for consideration/approval</p>

*Liverpool Interaction Database

**refer to resource for full details



Winnipeg Regional Health Authority
Office régional de la santé de Winnipeg

Tips for Pharmacists

- Medication history with patient crucial
- Consider consulting at least 2 drug interaction resources
 - Beware product monograph may not list drug interactions
- Interpret findings and identify management options for patient and prescriber
 - Read options fully to understand options are suitable for patient
 - Collaborate with the prescriber for safe patient use of Paxlovid™

Summary

- Paxlovid™ available in MB for the treatment of covid-19 in immunocompromised patients and at risk groups
- Paxlovid™ drug interactions most challenging aspect
 - Careful detailed drug interaction screening is required
- Pharmacists are in key position to identify and interpret drug interactions
 - Collaborative dialogue between physician and community pharmacist

Questions

