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New Brunswick College of Pharmacists
Ordre des pharmaciens du Nouveau-Brunswick

GUIDANCE:
ASSESSING AND PRESCRIBING FOR PAXLOVID

The New Brunswick College of Pharmacists thanks Continuing Professional Development for Pharmacy Professionals/MedSask for sharing their resources. Guidance is also included from Horizon Health's Firstline app (https://app.firstline.org/en/clients/230-horizon-health-network/steps/63287), and the corresponding app from Vitalité (https://app.firstline.org/fr/clients/367-vitalite-reseau-de-sante/steps/63361).

* Note: This guidance supports and provides resources for only the assessment and prescribing of **Paxlovid** (nirmatrelvir/ritonavir) for the treatment of mild to moderate symptoms of COVID-19.

INTRODUCTION

The New Brunswick College of Pharmacists (the College), in collaboration with the New Brunswick Department of Health (DoH), has authorized pharmacist assessment and prescribing for Paxlovid to facilitate access for eligible patients who have acquired SARS-CoV-2 (COVID). Changes have been made to regulations, the DoH has authorized funding, and resources are prepared, which will allow pharmacists to provide this service, when Paxlovid is a viable treatment option in the early management of COVID-19 infection.

Authority to consult and prescribe for treatment of mild to moderate symptoms of COVID-19 is given in Section 21 of the Regulations and under Appendix 2, "List of Minor Ailments." Pharmacists assessing and prescribing Paxlovid for COVID-19 must have met requirements for Minor Ailments and notified the College.[1]

The provision of any references and tools in this document does not preclude the use of other resources, provided they are consistent with Canadian best practice guidelines.

PRIOR TO INCORPORATING PAXLOVID ASSESSMENTS

Pharmacists must complete the Minor Ailments Declaration and meet requirements in the Minor Ailments document.[1] In addition, pharmacists are encouraged to add their names to the list of NB pharmacies offering this service by contacting New Brunswick Drug Plans via email at info@nbdrugs-medicamentsnb.ca or by calling NBPDP at 1-800-332-3691 (use the subject line "Pharmacist Assessment and Prescribing for Paxlovid". Include the pharmacy name, banner, address, and telephone number in the email).

To assess for and prescribe Paxlovid in the early treatment of COVID-19 infection, pharmacists must take the necessary steps to be competent. This should include but is not limited to:

- undertaking additional education;
- reviewing clinical guidelines; and
- researching primary literature.

Pharmacists must use their professional judgment in choosing to undertake prescribing. Sufficient knowledge of the patient's condition and clinical status is to be accessible prior to undertaking assessment and prescribing of Paxlovid.

[1] https://nbpharmacists.ca/legislation/practice-requirements/

When providing assessment and prescribing of Paxlovid, a pharmacist must recognize that they may be the only health-care provider that a patient sees regarding COVID-19 treatment. As such, pharmacists must use a patient-centred approach to provide:

- a comprehensive review of all treatments available for COVID-19, both pharmacological and non-pharmacological;
- patient education about the risks, management, and screening options for COVID-19;
- referral resources for treatment, in the event that the patient is not eligible for Paxlovid prescribed by a pharmacist;
- education regarding the importance of reducing risk of viral transmission; and
- other patient education resources

PATIENT ASSESSMENT AND PRESCRIBING

Public Health NB recommends the use of Paxlovid for symptomatic patients meeting eligibility criteria[2] at high risk of progression to severe disease. A thorough patient history[3] is required to determine the most appropriate treatment option. Assessment of symptomatic patients is intended to be conducted virtually, to decrease risk of viral transmission within the pharmacy.

Pharmacists must complete and retain the Nirmatrelvir/Ritonavir (Paxlovid) Eligibility Form in the patient's pharmacy record.

Assessment Process

Paxlovid is recommended for adults over 18 if they:

- have tested positive for COVID-19;
- have developed symptoms that began within the last five (5) days;
- are at higher risk of severe outcomes.

Positive COVID-19 test

- PCR (laboratory confirmed test)

[2] https://app.firstline.org/en/clients/230-horizon-health-network/steps/63422?navigator=eJyLjlZKz0yx0tcvLkhNLikqzdUPLkkt0DczNrIwV9LJK83JAROxsQAefw3G , under "Criteria for Use"

[3] https://app.firstline.org/en/clients/230-horizon-health-network/steps/63422?navigator=eJyLjlZKz0yx0tcvLkhNLikqzdUPLkkt0DczNrIwV9LJK83JAROxsQAefw3G, under "Clinical Assessment Process", steps 1 to 6

- Abbott ID[4]
- POCT (rapid antigen test)

Treatment window:

Within five (5) days of symptom onset

- Symptom onset: The date the case's symptoms started would be considered "Day 1".
    - For example: if symptoms started on February 2, this would be the "Date of Symptom Onset". February 6 would be day five (5) and final day they would be eligible for treatment.

Presenting symptoms:

Patients offered treatment should be appreciably symptomatic from COVID-19 and ONLY suffering from mild-to-moderate illness. (See reference[2])

Mild illness - refers to patients who have any of the typical signs and symptoms of COVID-19 but do not have increased work of breathing, dyspnea, reduced oxygen saturations or abnormal chest imaging (i.e. no signs of pneumonia).

- These patients can still progress to severe illness, especially if those symptoms are profound, or exist in combination, but the chance is lower than in moderate illness.
- Flu-like symptoms such as fever and diffuse myalgia are indicative of systemic illness and have been shown to be associated with higher risk of illness progression.
- In equivocal cases, a 24-hour followup period is reasonable, if still within the treatment window.
- Please note - immunocompromised, elderly or other vulnerable patients may not develop a more significant symptomology beyond mild illness but remain at high risk for developing severe disease.

Patients with moderate illness are more likely to progress to severe illness and should be offered therapy if criteria for use are met. Moderate illness refers to symptomatic illness with evidence of lower respiratory disease during clinical assessment or imaging but who still have an oxygen saturation (SpO2) ≥92% on room air and no signs of severe pneumonia (respiratory rate > 30 breaths/min, severe respiratory distress or SpO2 ≤92% on room air).

Eligibility criteria:

Patients may be considered eligible for Paxlovid if they:

- are not fully vaccinated;
- are an older adult, as risk increases with age;
- have one or more chronic medical conditions;
- are moderately to severely immunocompromised due to a medical condition or treatment.

[4] Note: Abbott ID is used by First Nations communities.

Depending on a patient's age and health status, they may still be considered at higher risk of developing severe outcomes even after having received all of the COVID-19 vaccine doses they are eligible for.

Exclusion criteria: The following patients are **not** eligible for treatment with Paxlovid:

- < 18 years of age; OR
- severe hepatic impairment (Childs Pugh C); OR
- history of clinically significant hypersensitivity reactions to its active ingredients or any other components of the product; OR
- co-administration with drugs that are highly dependent on CYP3A4 for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions; OR
- co-administration with drugs that are potent CYP3A4 inducers where significantly reduced nirmatrelvir/ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

Cases for Referral

Pharmacists are expected to use their professional judgment when making referrals. In the case a patient does not have a provider, patients may be directed to call 811 or visit https://www.evisitnb.ca/. The following provides criteria for when a patient should seek emergency services or be referred to another practitioner.

Emergency Referral: Patients who have moderate or severe symptoms may require hospitalization. These symptoms may include, but are not limited to:

- difficulty breathing or worsening of respiratory symptoms;
- greater than 30 breaths per minute;
- shortness of breath at rest or requiring supplemental oxygen;
- respiratory distress (difficulty speaking in full sentences, severe wheezing);
- severe dehydration, decreased urination, or significant reduction in food or fluid intake;
- tachycardia (heart rate greater than 100 beats per minute);
- persistent pain or pressure in the chest;
- lethargy, confusion, altered mental state, difficulty waking up.

Pharmacists may decide to refer these patients to another health-care provider after assessment.

Referral for assessment: Some patients may present with significant comorbidities and/or are taking medications which interact with Paxlovid, or after the five-day treatment window. These patients may be able to be managed by pharmacists, but others may need to be referred to their family physician/nurse practitioner, or specialist, in the case of HIV or transplant patients:

- > day five (5) since symptom onset;
- patients with HIV infection not currently on antiretroviral therapy, HIV infection with recent detectable viral load, AIDS-defining illness, CD4 count less than 200, or suspicion of uncontrolled HIV;

- patients with drug interaction(s) that have been deemed non-manageable by the community prescriber, but may be manageable by the specialists, such as transplant and cancer medications;
- immunocompromised by complex **disease** state:
    - active treatment for cancer;
    - hematopoietic stem cell transplant recipient;
    - solid organ transplant recipient;
    - moderate to severe primary immunodeficiency.

Managing drug interactions

Before prescribing nirmatrelvir/ritonavir, pharmacists should carefully review concomitant medications for drug interactions to reduce the risk of harm. While management of potential drug interactions will require attention, and a best possible medication history (BPMH) is a critical part of patient assessment, pharmacists have already been performing this medication management as part of dispensing of Paxlovid.

Background: Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent that has been used to boost HIV protease inhibitors. Coadministration of ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range. Because of ritonavir's inhibitory effect on the P450 system, other medications metabolized similarly will be impacted by co-administration with Paxlovid.

Ritonavir is a CYP3A4 inhibitor, and may decrease the metabolism of medications dependent on CYP3A4. In those medications that require CYP3A4 for clearance, elevated concentrations may occur. This could result in a serious or life-threatening reaction. In those medications that require CYP3A4 for activation, such as prodrugs, reduced concentrations may occur. This could result in a decreased therapeutic effect of the medication.

Nirmatrelvir and ritonavir are both CYP3A4 substrates, and CYP3A4 inducers may increase metabolism of Paxlovid. Potential for loss of virologic response and/or resistance, which may lead to treatment failure.

To consider: Additional patient factors that affect managing the drug interaction, such as:

- Does the patient understand which interacting medication to hold or to split the dose?
- Is the patient able to split the tablet themselves?
- Does the patient receive compliance packs which require manipulating?
- Does the patient comprehend when to restart their interacting medication?

Potential management strategies to facilitate the use of nirmatrelvir/ritonavir may differ depending on the magnitude and significance of the interaction. Options include:

- dose adjustment of the concomitant medication[5];

[5] Note that pharmacists are authorized to adapt a prescription, with regard to a dosage adjustment, under Regulation 21.3(a)(i). This includes controlled medications, as authorized in a Section 56 exemption.

- use of an alternative to the concomitant medication;
- increased monitoring for potential adverse reactions to the concomitant medication;
- temporary withholding of the concomitant medication.

These strategies should be considered for the five-day duration of nirmatrelvir/ritonavir treatment and for at least two (2) to five (5) days after treatment completion.

Please note, the onset of inhibition is rapid and clinically significant drug-drug interactions may occur despite the short treatment course.

Questions to consider:

- Is the patient taking or has taken a CYP3A4 enzyme inducer in the last 28 days (e.g., certain anticonvulsants, antineoplastics, a rifamycin, St. John's wort)?
    - *Do NOT prescribe nirmatrelvir/ ritonavir.*
- Is the patient taking an interacting drug with a long plasma half-life and narrow therapeutic window (e.g., certain antiarrhythmics, antipsychotics, antineoplastics), in that the interacting drug will persist in the body after the last dose and may still interact with nirmatrelvir/ritonavir?
    - *Do NOT prescribe nirmatrelvir/ritonavir even if the interacting drug can be held.*
- Is the patient taking an interacting drug that can be safely held?
    - *Hold the medication starting the first day of nirmatrelvir/ritonavir therapy and resume two (2) to five (5) days after the last dose of nirmatrelvir/ritonavir treatment depending on recommendations.*
- Is a specialist prescriber or pharmacist able to help adjust the dose or dosing interval, replace the drug with an alternative agent, manage side effects, and guide therapeutic drug monitoring?
    - *Consult a local specialist or pharmacist for advice and recommendation.*

Documentation

Section 21.14 of the Regulations outlines the requirements for documentation of the patient assessment and any subsequent treatment prescribed. Section 21.15 states that "the pharmacist, when prescribing a drug, treatment or device, will notify the client's primary care provider (when such exists) when the order the pharmacist is prescribing is clinically significant." Because of the clinical significance of a patient taking Paxlovid, the College's expectation is that notification of a family physician be done, when the patient has one.

The Nirmatrelvir/Ritonavir (Paxlovid) Eligibility Form must be retained as documentation.

RESOURCES

The following are resources that professionals may use when assessing and prescribing for Paxlovid. Information contained within such resources may not be applicable to New Brunswick Paxlovid criteria, professionals should use them to supplement the clinical assessment tools available in New Brunswick.

Drug interaction tools and resources:

- Horizon Health Firstline Clinical Decisions:
  - https://app.firstline.org/en/clients/230-horizon-health-network/steps/63422?navigator=eJyLjlZKz0yx0tcvLkhNLikqzdUPLkkt0DczNrIwV9LJK83JAROxsQAefw3G (see "Clinical Pearls: Managing Drug Interactions:)
- Vitalité Firstline Clinical Decisions
  - https://app.firstline.org/fr/clients/367-vitalite-reseau-de-sante/steps/63361
- Liverpool COVID-19 Drug Interaction Checker
  - https://www.covid19-druginteractions.org
- Liverpool COVID-19 Drug Interactions - Prescribing Resources
  - https://www.covid19-druginteractions.org/prescribing_resources
- BC COVID Therapeutics Committee (CTC) - Practice Tool #3: Drug-Drug Interactions & Contraindications
  - http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/treatments
- Nirmatrelvir/Ritonavir - What Prescribers and Pharmacist Need to Know (Ontario Science Table)
  - https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-2-0/
- Paxlovid for a Patient on a DOAC (Ontario COVID-19 Science Advisory Table and University of Waterloo School of Pharmacy)
  - https://covid19-sciencetable.ca/sciencebrief/paxlovid-for-a-patient-on-a-doac/
- NS Health Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool
  - http://policy.nshealth.ca/Site_Published/covid19/document_render.aspx?documentRender.IdType=6&documentRender.GenericField=&documentRender.Id=94353
- Statement on Paxlovid Drug-Drug Interactions COVID-19 Treatment Guidelines (nih.gov)
  - https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/

Suggested clinical tools:

- Paxlovid™ Product Monograph
  - https://covid-vaccine.canada.ca/info/paxlovid-en.html
- CPhA - Treatment of COVID-19 with Paxlovid™
  - https://www.pharmacists.ca/cpha-ca/function/utilities/pdf-server.cfm?thefile=/cpha-on-the-issues/Paxlovid-COVID19_EN.pdf
- Renal function calculators
  - https://globalrph.com/
- MedSask Guidelines for Prescribing Paxlovid:

    - https://medsask.usask.ca/professional-practice/paxlovid-hcp/prescribing-paxlovid-for-covid-19.php.
- Numerous Wrong Dose Errors with PAXLOVID - Institute For Safe Medication Practices: https://www.ismp.org/resources/numerous-wrong-dose-errors-paxlovid
- Quebec Présentation Clinique and Algorithme de Traitements
    - https://www.inesss.qc.ca/fileadmin/doc/INESSS/COVID-19/COVID_19_Outil_Paxlovid_VF.pdf
    - https://www.inesss.qc.ca/fileadmin/doc/INESSS/COVID-19/Algorithme_traitement_COVID_ambulatoire_VF.pdf
    - https://www.inesss.qc.ca/fileadmin/doc/INESSS/COVID-19/INESSS_OIPI_Paxlovid_VF.pdf

Educational Opportunities:

- Quebec Usage optimal de l'association nirmatrelvir/ritonavir (PaxlovidMC) en milieu ambulatoire
    - https://vimeo.com/691652559/b9f213691a
    - Slides: https://vimeo.com/691652559/b9f213691a
    - Q&A from AQPP: https://aqpp-monpharmacien-production.s3.ca-central-1.amazonaws.com/app/uploads/2022/04/01190537/PAXLOVID-Foire-aux-questions-et-boite-a-outils.pdf