Therapeutic Options for Mild to Moderate COVID-19 Patients

Questions and answers for health care providers

1. Where can I find an overview of the clinical guidance about new therapeutics for COVID-19?

The BC COVID Therapeutics Committee reviews the evidence and has created detailed guidance documents. For a comprehensive overview, please see the full guide developed by the BC COVID Therapeutics Committee: Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19

2. Will I be prescribing Paxlovid now?

In the early weeks, there was a relatively small volume of drugs available, so a staged approach was used to allow those who serve patients at greatest risk to prescribe early with support. Now, you have the opportunity to prescribe.

To enable prescribing and dispensing and evaluation of this new drug, a special prescription form has been developed on the Special Authority page where instructions are also posted on how to access Paxlovid for non-BC residents.

The direct link to the prescription:
https://www2.gov.bc.ca/assets/gov/health/forms/2368fil.pdf

It is recommended that you always go to the form on the website, rather than printing a supply of these.

3. Who are the treatments currently recommended for?

In alignment with recommendations from Public Health Agency of Canada (PHAC) and the Canadian Agency for Drugs and Technologies in Health (CADTH), these treatments are currently recommended for people who have an increased risk of hospitalization for COVID-19. The CTC has worked with BCCDC to obtain data on the absolute risk for hospitalization from Omicron (excluding those who are incidentally diagnosed) in patients in BC, and how age, vaccine status and co-morbidities impact this risk. Treatment is recommended in patients who have a 5% chance or greater of being hospitalized from COVID-19. Additionally, treatment is suggested in those who have a slightly increased hospitalization risk (3-4%). Taken together, the expanded eligibility criteria are

- Individuals who are immunocompromised or have high-risk conditions identified as Clinically Extremely Vulnerable (CEV) regardless of vaccine status or previous infection

    - *Not all children ages 12-17 who are CEV will benefit from treatment. Paxlovid is not recommended below the age of 18 at this time. Those with multiple co-morbidities would have the highest potential benefit and are eligible only for sotrovimab*
- Unvaccinated individuals without previous infection who are EITHER:
    - ≥50 years OR
    - have three or more chronic conditions/co-morbidities
- Individuals ≥ 50 years with 1-2 vaccine doses or previous infection alone, with three or more chronic conditions/co-morbidities
- Individuals aged ≥70 years with 1-2 vaccine doses or previous infection alone, with one or more chronic condition/co-morbidity
- Individuals ≥ 70 years with three or more chronic conditions/co-morbidities regardless of vaccine status or previous infection
- Indigenous individuals (if not captured above) who are EITHER:
    - unvaccinated without previous infection OR
    - ≥ 50 years with 1-2 vaccine doses or with previous infection alone OR
    - ≥ 70 years regardless of vaccine status or previous infection

To determine an individual's risk for hospitalization, see Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19

Pregnancy and Breastfeeding: Currently available therapies have not been evaluated in pregnancy or breastfeeding. Prescribers may consult Reproductive Infectious Disease on call at BC Women's Hospital if prescribing COVID-19 therapy, especially nirmatrelvir/ritonavir.

Patients are encouraged to use protection while taking these medications. In addition, those on oral contraceptives should use a back-up method when taking nirmatrelvir/ritonavir due to drug interactions leading to lower plasma levels of estrogen.

Pediatrics: nirmatrelvir/ritonavir (Paxlovid) is not currently available for children under 18 yrs. All cases in which sotrovimab is being considered should be discussed with, and approved by the Pediatric Infectious Diseases physician on call at BC Children's Hospital.

4. What are some of the contraindications?

- **Nirmatrelvir/ritonavir (Paxlovid)** should not be used in end-stage liver disease (Child-Pugh C), severe renal disease (eGFR < 30ml/min). In patients with hepatitis B and C, or HIV infection regardless of treatment status, Specialist Consultation (e.g., Infectious Diseases, HIV Specialist) is recommended, but should not delay treatment.
    - **Many drug-drug interactions contraindicate the use of nirmatrelvir-ritonavir**, most common include amiodarone, DOACs, statins, some antipsychotics, midazolam and triazolam, as well as illicit drugs; especially fentanyl and methamphetamine. Patients with hypersensitivity to ritonavir or other protease inhibitors should not be prescribed nirmatrelvir/ritonavir.

Drug interactions must be verified and a management plan in place before prescribing-*see Practice Tool #3: Drug Interactions and Contraindications

- **Sotrovimab** (Xevudy) is known to cause hypersensitivity reactions and infusion reactions, although they are rare. Sotrovimab is contraindicated in those who are hypersensitive to this drug or to any ingredient in the formulation: if reactions develop during the 1-hour infusion, the infusion should be stopped.

5. What are the symptom windows in which these antiviral therapies are most beneficial?

Symptom windows vary with each therapeutic agent and follow study inclusion criteria:

- Sotrovimab (Xevudy) should be given within 7 days of symptom onset
- Nirmatrelvir/ritonavir (Paxlovid) should be given within 5 days of symptom onset

**It is appropriate to allow the addition of adequate time for delivery of medication for those living in remote and rural communities*

6. Who can I call for help?

Call **COVID Antivirals Support Line for Clinicians and Pharmacists** if you have questions about drug interactions

A provincial pharmacy line has been established to support the arrival of the new COVID-19 anti-viral medications in BC, Paxlovid and sotrovimab. There are a few requirements that doctors need to know when it comes to prescribing, including the treatment window, how they contradict or interact with other medications, etc. In addition, a prescriber and/or a pharmacist must assess each prescription against drug interactions and medical contraindications. This provincial pharmacy line will support prescribing and pharmacists to dispense these novel medications.

For expert pharmacist advice, please call 1-866-604-5924 (Monday – Friday, 8:30am – 4:30pm). A clerk will answer your call (or leave a voicemail) and arrange a pharmacist to call you back. Calls will be responded to as soon as possible during office hours.

Be ready to provide:

- Clinician/pharmacist details: Name, phone number, city where you practice, and when is a good time to call you back.
- Patient details: Name, date of birth (DoB), personal health number (PHN), and any relevant medical info

7. Is there updated research on the effectiveness of Sotrovimab (Xevudy) for mild to moderate illness?

The following summarizes some key points from the BC CTC's clinical guidance document. It is expected that evidence will continue to develop and therefore be sure to watch for changes to this evidence. It's important to say that these studies were completed prior to Omicron, and therefore we will be watching to learn more about the efficacy of this new therapy as it becomes available:

- Sotrovimab is a monoclonal antibody with retained activity against Omicron. It's ability to neutralize the BA.2 variant, which is becoming more prevalent in BC, is reduced. However, preliminary data show that at its current dose, sotrovimab still successfully neutralizes BA.2. In vivo results are forthcoming, and the CTC is actively monitoring the available evidence.
- There has been a single peer-reviewed double blind randomized placebo-controlled manufacturer sponsored trail (COMET-ICE). Prior to Omicron, 1057 unvaccinated outpatients with mild-moderate symptoms and at least one risk factor of disease progression (e.g. age >60, obesity, hypertension, diabetes) were randomized.
- They received a 500mg IV infusion compared to placebo within 3-7 days of symptom onset.
- The primary endpoint was a composite outcome of all-cause hospitalization for >24 hours or death within 29 days of receipt of infusion.
- Results: 6/528 patients met the primary outcome in the treatment group compared to 30/529 in the placebo group (1% vs 6%), with an absolute risk reduction of 5% and Number-Needed-To-Treat of 20. There were two deaths, both in the placebo arm.
- Secondary outcome showed reduced progression to severe respiratory disease of 1% vs 5% on the basis of symptoms.
- Sotrovimab did not reduce the length of stay or ICU- bed days.
- 6 patients in each group had infusion reactions.
- While all the study participants were >18 years, the manufacturer has submitted sufficient pharmacokinetic and pharmacodynamic data to Health Canada to authorize inclusion of patients 12-17y weighing at least 40kg.

8. Is there updated research on the effectiveness of Nirmatrelvir/Ritonavir (Paxlovid) for mild to moderate illness?

The following summarizes some key points from the BC CTC's clinical guidance, and the landmark trial of Paxlovid (EPIC-HR) which was published in February 2022 in the New England Journal of Medicine. It's important to say that these studies were completed prior to Omicron, and therefore we will be watching to learn more about the efficacy of this new therapy as it become available:

- This medication is a direct-acting anti-viral made up of two agents. It belongs to the protease inhibitor (PI) class and is similar to PIs used to treat HIV

- Nirmatrelvir/ritonavir was studied in a double-blind placebo-controlled trial, "EPIC-HR" of 2246 unvaccinated outpatients with mild to moderate COVID-19 within 5 days or less of symptom onset.
- Participants deemed at risk of disease progression to requiring hospitalization were enrolled. This included unvaccinated individuals who were either 55 years or older or who had a chronic condition such as hypertension, diabetes, lung disease or obesity. The median age of participants in the trial was 46 and the most common risk factor present was smoking, followed by hypertension. Patients were excluded if they had any potential drug-drug interactions.
- The primary endpoint was COVID-19 related hospitalization (not all cause) or death from any cause.
- Results: 0.8% (approximately 1%) (8/1039) patients in the treatment group vs 6.3 % (66/1064) in the placebo arm experienced the primary endpoint (nearly all events were hospitalizations and not death). Therefore, the absolute risk reduction is 5.5% (with a relative risk reduction of 88%) and a Number-Needed-to-Treat of 18.
- The rate of hospitalization from any cause and the rate of mortality has not yet been reported.
- Drug has been shown to cause nausea, diarrhea and taste disturbances more frequently than placebo, with an adverse effect rate attributed to drug vs. placebo of 7.8% vs. 3.8% respectively

9. What are some of the challenges in prescribing Paxlovid?

Patients who are COVID-19 positive and in the first 5 days of their symptoms can be considered for Paxlovid, or sotrivamab if that is more appropriate.

One of the challenges is that for those who potentially have the greatest benefit from Paxlovid, there are also risks with respect to prescribing related to their underlying disease and drug-drug interactions with their medication.

While there is evidence of benefits, Paxlovid has many drug-drug interactions, some of which are serious. This includes drugs such as immunosuppressants used in transplant, some cancer drugs and more common drugs such as anti-coagulants, statins and others. There are also serious consequences with the use of opioids that must be considered. Additionally, the patient's renal function must be considered and the medical risks and benefits of potentially holding or reducing the dose of some of their usual medications to facilitate the use of Paxlovid. This means that prescribing this medication requires careful review of the patient, their symptoms, the risk of COVID-19 and the risk of interactions or alterations to their current medications and discussion of those risks with the patient. See the Practice Tool #3 – Drug-drug Interactions to learn more about these considerations.

10. How will my high-risk patients get access?

Any clinician can now prescribe. If you have patients who are clinically extremely vulnerable or within the high-risk category, start having conversations with them now about what treatment options are available.

11. What type of testing is required?

A positive test result is required. Polymerase Chain Reaction (PCR) is the preferred diagnostic test, especially in the first 1-2 days of symptoms when a RAT is more likely to be falsely negative. However, a positive Rapid Antigen Test (RAT) is acceptable.

12. Do patients need to be symptomatic?

Yes. Patients offered treatment should be appreciably symptomatic from COVID 19. Treatment is unlikely to benefit those who are mildly ill and improving on their own. Therapies should not be prescribed to asymptomatic patients.

A great deal of case-by-case clinical judgement is required to discern whether mild symptoms warrant treatment.

Patients who are moderately ill, i.e., showing evidence of lower respiratory disease during clinical assessment such as shortness of breath or imaging suggestive of pneumonia, are the most likely to progress to severe illness.

13. Are there any materials to help me counsel my patients on antiviral therapies?

Patient information sheets for both sotrovimab (Xevudy) and nirmatrelvir/ritonavir (Paxlovid) are available on the BCCDC website: http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/patient-handouts

- Patient Information about Paxlovid
- Patient Information about sotrovimab

In addition, there is a self-screening tool posted publicly that allows patients to find out if they might benefit from COVID-19 antiviral therapies.

Materials for providers:

- Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19
- Provider Summary
- Practice Tool 1 – Assessment Steps
- Practice Tool 2 – CEV Definitions

- Practice Tool 3- Drug Interactions and Contraindications
- Standardized Paxlovid Rx

14. What do I need to know about monitoring and evaluation?

Patients should call you back if they have any concerns. With the newness of this drug, BC has taken the proactive approach of contacting all patients who receive Paxlovid over the next three months to follow-up with each patient: identifying whether there were adverse drug events, compliance with the 5-day treatment course, and patient outcomes. This evaluation will provide us with useful information as we learn more about Paxlovid and future COVID therapies.