How to Use this Guide

This guide is a step-by-step clinical assessment tool for clinicians such as physicians, pharmacists and nurse practitioners who are directly involved in assessment and management of patients with mild-moderate COVID-19. Additional materials have been developed to accompany this tool, and include:

- **The Clinical Practice Guide**, a comprehensive guide with recommendations and supporting evidence
- **Practice Tool #2 – Definitions of Clinically Extremely Vulnerable** criteria
- **Practice Tool #3 – Drug-drug Interaction and Contraindication** management tool

In this Tool you will find:
1. [Who can prescribe](#) and centralized prescribing through [Service BC](#) (811)
2. [Expanded eligibility criteria](#) including the patient [self-screener](#)
3. How to determine [risk of hospitalization](#)
4. [Recommendations](#) for treatment based on risk – and if treatment is being pursued:
6. [Assessing vaccine](#) or previous infection status
7. Establishing [symptoms and progression](#)
8. Calculating [treatment window](#)
9. Assessing contraindications
10. Assessing and managing [drug-drug interactions](#) (including how to access the [pharmacy support line](#))
11. Peer-peer physician support including for [pregnant women, pediatrics](#) and ID
12. [PAXLOVID Prescription](#) link and [pharmacies that carry PAXLOVID](#)
13. [Referring for remdesivir](#) to the Health Authorities
14. [Patient counselling and resources](#)

This guide is intended to be practical and was developed clinicians who routinely care for patients with COVID-19. It should not replace clinical judgement.

### Step-by-step ASSESSMENT

**1. Who Can Prescribe and Centralized Prescribing**

At this time, anyone with a license to prescribe can prescribe nirmatrelvir/ritonavir.

Patients are encouraged to make an appointment with their primary care provider for COVID-19 treatment. There may be cases where patients who have a primary care provider are not be able to get an appointment quickly enough to meet the 5-day treatment window. Furthermore, patients may not have a primary care provider, or the primary care provider may not be comfortable with nirmatrelvir/ritonavir.
In these situations, patients should be advised to call Service BC at 1-888-COVID19

They will be screened by an agent for eligibility and if they qualify, put through to a centralized line staffed by physicians and pharmacists dedicated to COVID assessment and treatment (CATe line). This line is for patients only; different resources such as a pharmacy consultative services are available to prescribers (see 10).

Patients who call the office asking for an appointment for COVID-19 therapy can be first directed to the Self-Screener to see if they qualify. The patient can be advised to go to www.covidtreatments.gov.bc.ca, google “COVID-19 Therapy Self-Assessment Screen” or call 1-888-COVID19 if they would rather talk to an agent. The Self-Screener will guide the patient in determining if they have received the appropriate testing, verify that they are symptomatic and take them through the basic eligibility criteria.

2. Verify Treatment Eligibility Criteria and Self-screener

Current eligibility criteria have been developed using BC data that assesses risk of hospitalization from Omicron based on age, vaccine status and number and type of at-risk conditions. For precise risk estimates using thermal maps or to find out how these criteria were developed, see the Clinical Practice Guide.

- Immunocompromised individuals\(^1,2\) and those with high-risk conditions\(^3\) identified as Clinically Extremely Vulnerable Group 1\(^1\), Group 2\(^2\), and Group 3\(^3\) (CEV 1, CEV 2, and CEV 3), regardless of vaccine status or previous infection. (See also Practice Tool 2 – CEV Definitions).
- 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

*Chronic conditions are broad include any prolonged problem that requires treatment, monitoring or follow-up, e.g., obesity, smoking, diabetes, heart failure, heart disease, stroke, neurological conditions, frailty, cognitive issues, mobility barriers etc.

1. CEV 1: severe immunocompromise due to, e.g., solid organ transplant, bone marrow or stem cell transplant, treatment for hematological malignancy, receiving anti-CD20 or B-cell depleting therapies
2. CEV 2: moderate immunocompromise due to e.g., receiving immunosuppressive agents, moderate-severe primary immunodeficiency, cancer treatment for solid tumors, advanced or untreated HIV
3. CEV 3: e.g., cystic fibrosis, severe asthma or COPD, diabetes requiring insulin, intellectual and developmental disabilities, rare blood disorders, dialysis, neurological conditions requiring Bi-PAP or chronic ventilation, cancer not captured above
Patients can also access a self-screener online (or by calling 1-888-COVID19 if they’d rather speak to a Service BC service agent) to see if they meet the eligibility criteria above.

CEV Criteria:
- Patients who are classified as CEV have received a letter from Dr. Bonnie Henry or communication from Public Health and usually know who they are
- CEV status may make them eligible but consult Practice Guide #2 – CEV Definitions to make sure the patient is still vulnerable. For example, if the patient’s cancer treatment ended or if some time has passed since the receipt of their immunosuppression drugs, they are no longer at risk. Pay attention to dates in the guide. They still qualify for vaccine boosters and their CEV status is not revoked; their risk has simply decreased to the point where treatment may not be needed
- Pediatric patients and pregnant patients who are in the CEV category require consultation with a BCCH or BCWH specialist; use the on-call contact information and refer to the pregnancy and pediatric sections below

Indigenous Status:
- Patients can self-identify
- Indigenous individuals face social determinants of health (e.g., remote location, lack of access to culturally appropriate care, housing and food insecurity) that increase their risk of hospitalization and death from COVID-19 similarly to age-matched non-Indigenous individuals with multiple chronic health conditions

Chronic Conditions/Co-morbidities
- A large cohort study in BC showed that many conditions put patients at risk for hospitalization from COVID-19 and disease progression
- Conditions should be chronic, and generally require medical treatment or follow-up
- Co-morbidities/chronic conditions that were shown to increase risk of hospitalization include:
  - Neurological conditions such as epilepsy, dementia, multiple sclerosis, neuropathy
  - Psychiatric conditions such as schizophrenia, bipolar disorder, mania
  - Substance use disorders like opioid addiction, alcoholism
  - Disabilities such as intellectual developmental disability
  - Liver and kidney disease
  - Cardiovascular conditions such as arrhythmia, congestive heart failure, hypertension, stroke
  - Diabetes treated with medication
  - Rheumatic diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, lupus
  - Ulcerative colitis or Crohn’s
  - Asthma, COPD, bronchiectasis
  - Pregnancy
- Most other risk factors may be considered at the discretion of the clinician, for example:
  - Frailty
  - Malnutrition
  - Smoking
  - Obesity
  - Cognitive impairment
Serious social determinants of health such as homelessness may be considered - Conditions that are likely not serious enough to qualify may include transient issues that do not require regular treatment, follow-up or monitoring or mild issues; clinical judgement is required - This list is a guide only, use clinical judgement and assess the risk in a comprehensive manner, using age, vaccine status and co-existing conditions together.

This document provides guidance only; patients defined above are those who may benefit from treatment – case-by-case assessment is still required, and the totality of risk factors needs to be considered when offering treatment.

2. Assess the Risk of Hospitalization from Omicron

Risk can be estimated using a scoring system below. The risk assessment is important because it helps with informed decision making. Based on trial evidence, data support treatment in those who have a risk of ≥5%. It is reasonable to offer treatment to those with a lower risk (3-4%), but the magnitude of the benefit and the benefit vs. risk balance is not fully known; treatment can be forgone within this risk category if treatment poses significant safety issues with drug-drug interactions.

This scoring system accurately predicts the risk category from the BC-specific analysis 98% of the time and is 100% concordant with the CTC overall eligibility criteria.

<table>
<thead>
<tr>
<th>Point Scoring to Estimate Hospitalization Risk</th>
<th>Legend: Estimated Hospitalization Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (select ONE)</strong></td>
<td>3 points or less: No increased risk; treatment is not recommended</td>
</tr>
<tr>
<td>70+</td>
<td>4 points: Slightly increased risk (3-4%); treatment is suggested</td>
</tr>
<tr>
<td>50-69</td>
<td>5 points: Increased risk (5-9%); treatment is recommended</td>
</tr>
<tr>
<td>&lt;50</td>
<td>6 points or more: Highest risk (≥ 10%); treatment is recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine Status (select ONE)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated AND no previous infection</td>
<td>3 points or less: No increased risk; treatment is not recommended</td>
</tr>
<tr>
<td>Vaccinated with 1 or 2 doses OR previous</td>
<td>4 points: Slightly increased risk (3-4%); treatment is suggested</td>
</tr>
<tr>
<td>infection alone</td>
<td>5 points: Increased risk (5-9%); treatment is recommended</td>
</tr>
<tr>
<td>Vaccinated with booster (3-4 doses) OR</td>
<td>6 points or more: Highest risk (≥ 10%); treatment is recommended</td>
</tr>
<tr>
<td>previous infection + any vaccination</td>
<td></td>
</tr>
</tbody>
</table>

At-Risk Conditions (select ONE with the highest value)

| CEV 1 (Severe Immunocompromise)               | |
| CEV 2 or CEV 3                               | |
| Indigenous                                    | 6 points or more: Highest risk (≥ 10%); treatment is recommended |
| 3+ chronic conditions/risk factors            | |
| 1-2 chronic conditions/risk factors           | 4 points: Slightly increased risk (3-4%); treatment is suggested |
| no chronic conditions or risk factors         | 5 points: Increased risk (5-9%); treatment is recommended |

Add the points from the three sections

*Chronic conditions/risk factors can include for example obesity, smoking, diabetes, heart failure, liver disease, heart disease, stroke, frailty, mental health issues, and many others at the discretion of the treating clinician

1. CEV 1: severe immunocompromise due to, e.g., solid organ transplant, bone marrow or stem cell transplant, treatment for hematological malignancy, receiving anti-CD20 or B-cell depleting therapies
2. CEV 2: moderate immunocompromise due to e.g., receiving immunosuppressive agents, moderate-severe primary immunodeficiency, treatment for solid tumors, advanced HIV
3. CEV 3: e.g., cystic fibrosis, severe asthma or COPD, diabetes requiring insulin, intellectual and developmental disabilities, rare blood disorders, dialysis, neurological conditions requiring Bi-PAP/chronic ventilation, cancer not captured above
For more discussion on BC-specific data, the risk models and thermal maps, see Clinical Practice Guide, section on Local Data and Risk Models (pg. 4).

Expected Benefit
Based on trials of therapies for mildly-moderately ill patients, treatment is likely to decrease risk from ~5% to ~1%, for an ARR of 4% and an NNT of 25 to prevent one hospitalization. It is unknown how treatment impacts hospitalization in those whose risk is lower (e.g., 3-4%). In subgroups of lower-risk individuals, risk is never completely eliminated and rarely drops to less than 1%. In this group, treatment is likely to have an absolute risk reduction of 2-3% with an NNT to prevent one hospitalization between 35-50.

3. Follow Recommendations

Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days (150/100mg PO BID x 5 days in eGFR 30-60ml/min) is recommended within 5 days* of symptom onset to patients with a 5% or greater risk^ for hospitalization or progression to severe COVID-19

OR, if nirmatrelvir/ritonavir cannot be given to patients with a 5% or greater risk due to drug-drug interactions or contraindications (See Practice Tool 3 – Drug Interactions and Contraindications)

Remdesivir 200mg IV on day 1, followed by 100mg IV on days 2 and 3 (200mg IV on day 1, followed by 100mg IV 48-72 hours later in eGFR <30ml/min) is recommended within 7 days of symptom onset as an alternative to nirmatrelvir/ritonavir

Nirmatrelvir/ritonavir 300/100mg PO BID x 5 days (150/100mg PO BID x 5 days in eGFR 30-60ml/min) is suggested within 5 days of symptom onset to patients with a 3-4% risk^ of hospitalization or progression to severe COVID-19. As treatment effect is not directly known in this population, the estimated benefit needs to be weighed against potential risk of adverse effects in consideration with patient’s values and preferences

Due to a limited drug supply, operational constraints and unclear benefit in lower risk individual, patients with a risk of 5% or greater are currently being prioritized and offered treatment with remdesivir.

^To calculate risk, use the point system in Step 2. or consult the Clinical Practice Guide to use a thermal risk map
*The symptom window can be extended to 7 days in patients with a 5% or greater risk if they would otherwise be referred for remdesivir solely based on its longer treatment window

Notes:
1. THERE IS NO INDICATION TO COMBINE THESE THERAPIES: Due to drug scarcity and limited additional benefit, patients should receive ONE COVID-19-specific therapy.
2. For discourse on other therapies that are not routinely recommended and for a summary of evidence that informs all recommendations, see the Clinical Practice Guide

Sotrovimab has demonstrated reduced neutralization against various BA.5 sub-variants although it may retain some activity. If sotrovimab is used as a last line agent where potential of benefit outweighs the risk, disclosure to patients of risks and benefits in consideration of individual circumstances (clinical status, patient values, logistics) is necessary. Sotrovimab should not be chosen solely for convenience reasons.
4. Ensure Patient has Confirmed COVID-19 Infection - Testing

**Patients who are eligible for treatment are those who test positive for COVID-19 via a Polymerase Chain Reaction (PCR) or Rapid Antigen Test (RAT) test.** Most patients present for treatment as a result of a RAT. RATs are less sensitive in the first 24-48 hours of symptoms, but sensitivity increases on days 3-4, and with repeat testing it parallels that of a PCR test.

New testing guidelines issued by the BCCDC were written in collaboration with the CTC and focus on a RAT-based test-to-treat strategy. Patients are encouraged to self-administer a RAT as soon as they have symptoms. A positive RAT test does not require confirmation by PCR to proceed with treatment. A negative RAT should be repeated every 24 hours if it remains negative and symptoms persist, until the end of the 5-day treatment window is reached. Clinicians can also order a PCR at their discretion, for example in high-risk patients (e.g., CEV 1) who remain negative via RAT but the clinical suspicion is very high. Treatment may also be started empirically while awaiting PCR results. For information about how to order a PCR test, see [http://www.bccdc.ca/health-info/diseases-conditions/covid-19/testing/where-to-get-a-covid-19-test-in-bc#pcr](http://www.bccdc.ca/health-info/diseases-conditions/covid-19/testing/where-to-get-a-covid-19-test-in-bc#pcr).

Testing information is update regularly at [http://www.bccdc.ca/health-info/diseases-conditions/covid-19/testing](http://www.bccdc.ca/health-info/diseases-conditions/covid-19/testing). This website provides practical information for patients and providers alike.

**Practical Considerations:**
- Ensure the test was done recently, was administered correctly and that it is in fact positive
- Epidemiologically linked cases (e.g., household contacts of those who test positive) who have not been confirmed via COVID-19 testing should not be offered treatment. Encourage such patients self-administer a RAT to see if they are positive with COVID-19
- For more information on testing performance, see [Clinical Practice Guide](#)

5. Verify Vaccination Status

Unvaccinated/non-immune refers to the receipt of 0 vaccine doses and no history of previous infection. High risk patients do not have optimal protection from a 1 or 2 vaccine doses; a boosted regimen is considered ideal. Previous infection does not confer protection from hospitalization that offered by full vaccination with a booster(s); however previous infection combined with vaccination can be considered as adequate immunity.

**Practical Considerations:**
- The last vaccine dose should have been given 14 days ago or longer to be counted
- Although the “AstraZeneca”, “Pfizer” and “Moderna” vaccines are the most common vaccines, many patients in BC received other vaccinations and know them under different names.
- One Janssen vaccine dose necessitated one mRNA vaccine dose to complete a boosted immunization regimen
- Verity is a name of the Canadian distributor of the AstraZeneca vaccine, it shows up as “Verity”
- Some patients were immunized outside of Canada; those vaccines are clinically acceptable and count towards their immunization status
- Waning of vaccine efficacy has been observed; however not enough follow-up has been conducted
to appreciate the impact of long-term (>6 months) waning on hospitalization from Omicron. Most patients who have received a booster have received it in the last 3 months, especially with BC offering 4th doses. Waning is likely not significant if any booster doses have been received in the last 3-4 months
- In this guide, regimens with either 3 or 4 doses (1 or 2 boosters) are being referred to as boosted regimens
- Many who have received 1 or 2 doses have received them more than 6 months ago, and hence their risk of hospitalization is higher
- Clinical judgement is required when assessing a patient who has received a first or second vaccine dose in the last 3 months or who has had multiple COVID-19 infections; the risk of hospitalization of such patients is likely lower

Examples of vaccine and infection combinations

<table>
<thead>
<tr>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3 or 4</th>
<th>Vaccination status for treatment assessment of increased-risk individuals (3%+ risk of hospitalization)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td>mRNA</td>
<td>mRNA</td>
<td>Adequately Vaccinated with Booster(s)</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>AstraZeneca</td>
<td>mRNA</td>
<td>Adequately Vaccinated with Booster(s)</td>
</tr>
<tr>
<td>Janssen</td>
<td>mRNA</td>
<td>mRNA</td>
<td>Adequately Vaccinated with Booster(s)</td>
</tr>
<tr>
<td>Verity</td>
<td>AstraZeneca</td>
<td>mRNA</td>
<td>Adequately Vaccinated with Booster(s)</td>
</tr>
<tr>
<td>Verity</td>
<td>mRNA</td>
<td>mRNA</td>
<td>Adequately Vaccinated with Booster(s)</td>
</tr>
<tr>
<td>Janssen</td>
<td></td>
<td></td>
<td>Inadequately vaccinated without a booster – 2 doses</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td></td>
<td></td>
<td>Inadequately vaccinated without a booster – 2 doses</td>
</tr>
<tr>
<td>mRNA</td>
<td>AstraZeneca</td>
<td></td>
<td>Inadequately vaccinated without a booster – 2 doses</td>
</tr>
<tr>
<td>Verity</td>
<td>AstraZeneca</td>
<td></td>
<td>Inadequately vaccinated without a booster – 2 doses</td>
</tr>
<tr>
<td>Verity</td>
<td>mRNA</td>
<td></td>
<td>Inadequately vaccinated without a booster – 2 doses</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td></td>
<td></td>
<td>Inadequately vaccinated without a booster – 1 dose</td>
</tr>
<tr>
<td>Verity</td>
<td></td>
<td></td>
<td>Inadequately vaccinated without a booster – 1 dose</td>
</tr>
<tr>
<td>Infection</td>
<td>Any vaccine</td>
<td></td>
<td>Adequately Immune</td>
</tr>
<tr>
<td>Any vaccine</td>
<td>Infection</td>
<td></td>
<td>Adequately Immune</td>
</tr>
<tr>
<td>Infection</td>
<td>Infection</td>
<td></td>
<td>Inadequately Immune – Infection alone</td>
</tr>
<tr>
<td>Infection</td>
<td>Infection</td>
<td></td>
<td>Inadequately Immune – Infection alone</td>
</tr>
</tbody>
</table>

Previous infection with other variants (e.g., Delta) has shown to be insufficiently protective from re-infection with Omicron. Vaccination is recommended in those with previous infection history by Public Health and National Advisory Committee on Immunizations.

However, the risk of hospitalization or ICU admission has been observed to be low in those with previous infection in BC. For example, a study in the NEJM published February 2022 showed that effectiveness of previous infection against Omicron with any variant was 90.2%. Furthermore, epidemiological data from South Africa showed that the hospitalization risk went down significantly in the Omicron wave, despite that only ~40% of the population was vaccinated. The low hospitalization rate was attributed in part to a large proportion of patients being previously infected, and very small numbers of re-infected patients developed
Precise data on the severity of disease with reinfection in BC is forthcoming. As a 3- or 4-dose series is considered optimally immunized for the purposes of treatment eligibility assessment, previous infection alone in this highest-risk group is still considered inadequate protection from hospitalization. Patients who have a history of previous infection without any vaccination meet the under-vaccinated definition in this guide. Previous infection plus one vaccine dose, either before or after infection, is considered adequately immune.

6. Establish Symptoms and Symptom Progression

COVID-19 Mild and Moderate illness categories were developed by the WHO and focus on lower respiratory symptoms and oxygenation status of the patient. Patients offered treatment should be appreciably symptomatic from COVID 19.

Asymptomatic or no longer symptomatic patients should not be offered treatment. This includes patients who were symptomatic at the time of testing but have improved, or those who tested positive as part of screening (e.g., during travel, in the case of an outbreak or at the time of hospitalization). Vague or non-specific symptoms require a great deal of clinical judgement, especially in vulnerable patients (e.g., confusion, a fall, gastrointestinal symptoms) Prophylactic or pre-emptive treatment should NOT be offered. Follow-up is reasonable in patients who would qualify for treatment if otherwise symptomatic. Patients in whom the diagnosis of COVID-19 is not clear from their symptomatology should be referred appropriately.

Mild illness refers to individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have increased work of breathing, dyspnea, reduced oxygen saturations or abnormal chest imaging. 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. Great deal of case-by-case clinical judgement is required to discern whether mild symptoms warrant treatment. In equivocal cases, a 24–48-hour follow-up period is reasonable, if still within the treatment window.

Moderate illness refers to evidence of lower respiratory disease during clinical assessment or imaging but who still have an oxygen saturation (SpO2) ≥94% on room air. Oxygen saturation of <94% usually necessitates supplemental oxygen support and is classified as severe illness. Patients with moderate illness are more likely to progress to severe illness and can be offered therapy.

Illness trajectory is a useful in establishing progression of COVID-19. Patients who are visibly deteriorating are more likely to become severely ill. Treatment is unlikely to benefit those who are mildly ill who are clearly improving on their own. Treatment should not be given to asymptomatic or minimally symptomatic patients.

7. Calculate the Time since Symptom Onset
Symptom windows vary with each therapeutic agent and generally follow study inclusion criteria. **Remdesivir** (and if used in rare cases, sotrovimab) **should be given within 7 days of symptom onset** whereas for **oral antivirals should be given within 5 days. It is appropriate to allow the addition of adequate time for drug delivery for those living in remote and rural communities.** To facilitate the receipt of oral therapy in the highest risk patients (5% or greater), the nirmatrelvir/ritonavir treatment window can be extended to 7 days if the patient would otherwise be referred for remdesivir based solely remdesivir’s longer treatment window (i.e., the patient exceeds the 5-day window but is within the 7-day window).

Many patients do not recall when the first developed symptoms. Questions such as “How did you feel when you got tested?”, “What made you call for your test appointment” can be useful.

If patients have passed their symptom window, they can be reassured that in most cases, they would have already cleared the virus from their nasopharynx and have mounted an antibody response. Therapies like antivirals and antibodies have no additional impact. **There is little clinical rationale for extending the treatment window in practice and such practice cannot be routinely recommended in a general guide.**

Patients who have had prolonged symptoms or more or protracted illness despite recently testing positive for COVID-19 may require a clinical assessment of the illness trajectory to rule out other causes responsible for their symptoms. Patients are encouraged to get tested as soon as possible after COVID symptoms appear to avoid conflating persistent symptoms with COVID-19 infection. Patients who are immunocompromised or very elderly may not have symptoms that are clinically typical and may have protracted courses of illness. Judgement is required in such cases.

**Note on Patient Location**

This guide refers to patients based on their symptoms and not their physical location.

While mildly-moderately ill patients are usually outpatients recovering at home, patients can reside in Long-Term Care, present to the emergency department, or be hospitalized. Hospitalized patients who are mildly-moderately ill may be hospitalized for other reasons and incidentally diagnosed, be part of nosocomial outbreaks, or be hospitalized for COVID-related complications (e.g., a fall or dehydration), but still be mildly-moderately ill on the basis of their respiratory status. The receipt of systemic corticosteroids or baricitinib for the treatment of COVID-19 means that the patient’s severity of symptoms is beyond mild-moderate and antiviral or monoclonal antibody treatment should not be offered.

*The recommendations in this Guide apply to all patients irrespective of their physical location.*

**8. Assess Contraindications**

Nirmatrelvir/ritonavir has an extensive list of contraindications. Consult the accompanying **Practice Tool #3 – Drug Interactions and Contraindications.**

Most common contraindications with nirmatrelvir/ritonavir include:

- Severe renal disease (eGFR < 30ml/min or dialysis) – remdesivir is an option for these patients
• End-stage liver disease (Child-Pugh C or decompensated cirrhosis)
• In patients with hepatitis B and C, or HIV infection regardless of treatment status, Specialist Consultation (ID, HIV GP or GI) is recommended but treatment should not be delayed or withheld
• Patients with hypersensitivity to ritonavir or other protease inhibitors should not be prescribed nirmatrelvir/ritonavir.
• Many drug-drug interactions contraindicate the use of nirmatrelvir-ritonavir. Some can be held depending on the clinical scenario. The most common ones include:
  o **Novel anticoagulants rivaroxaban and apixaban:** switching the patient to dabigatran is recommended in some circumstances. A Special Authority coverage category has been arranged for this indication for 10 days while taking nirmatrelvir/ritonavir. Patient should be provided with a prescription. The dose of dabigatran depends on their renal function and if not known, age. (see Practice Tool #3 – Drug Interaction and Contraindications)
    (The 10-day dosing regimen of dabigatran has been simplified in consultation with thrombosis experts)

<table>
<thead>
<tr>
<th>eGFR or renal function available:</th>
<th>eGFR ≥60</th>
<th>dabigatran 150 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR 30-49</td>
<td></td>
<td>dabigatran 110 mg BID</td>
</tr>
<tr>
<td>eGFR &lt;30</td>
<td></td>
<td>do not use dabigatran.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR or renal function unknown:</th>
<th>age &lt; 75</th>
<th>dabigatran 150 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>age &gt;75</td>
<td></td>
<td>dabigatran 110 mg BID</td>
</tr>
</tbody>
</table>

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.

  o **NEW: Apixaban 5mg PO BID:** Recent data support a dose reduction for apixaban 5mg PO BID to 2.5mg PO BID for 7 days (i.e., the duration of the Paxlovid treatment and 2 additional days). This option may be used if switching to dabigatran is not feasible.
  o **Antiarrhythmics** like amiodarone and dronedarone: Holding the medication may be considered due to prolonged half-lives and restarted 2 days after nirmatrelvir/ritonavir treatment finishes
  o **Statins** like lovastatin or simvastatin: Lipid lowering agents can be held for 5 days during treatment with nirmatrelvir/ritonavir and restarted 2 days after treatment finishes
  o **Some antipsychotics** like clozapine that are hard to adjust, or injectable quetiapine
  o **Inhaled salmeterol;** holding salmeterol during a respiratory illness may not be possible but an alternative inhaler (e.g., salbutamol) could be considered
  o **Antiepileptics** such as carbamazepine and phenytoin are contraindicated and due to prolonged enzyme induction, there are no modification options
  o **Opioids especially fentanyl;** patients who use drugs need to be very carefully selected based on the risk of overdose, counselled and monitored

Remdesivir is contraindicated in those with demonstrated hypersensitivity to the product or any of its ingredients. Remdesivir should not be used in patients with ALT ≥5 times the ULN. The pharmacokinetics and safety of remdesivir in hepatic impairment have not been evaluated; expert consultation is recommended. Remdesivir is not officially approved in renal disease or dialysis; however, it has been widely used and deemed safe in this population.
Sotrovimab 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.

9. Assess/Manage Drug-Drug Interactions (pertains to nirmatrelvir/ritonavir); use Pharmacy Support

Nirmatrelvir and ritonavir have significant drug-drug interactions. Some drug-drug interactions can be managed. Clinicians must take a Best-Possible Medication History and review drug-drug interactions and provide patient counselling see Practice Tool 3 – Drug Interactions and Contraindications. Please note that some medications may not be on PharmaNet (e.g., anti-cancer drugs).

The most comprehensive resource for DDI assessment with nirmatrelvir/ritonavir is available from the University of Liverpool at https://www.covid19-druginteractions.org/checker. No resource contains 100% of the drug-drug interactions. Check an additional resource (e.g., LexiComp) for drug-drug interactions not listed on the University of Liverpool website.

Pharmacy Support is available for prescribers. Please contact community pharmacists (preferably the pharmacy that will dispense Paxlovid for the patient) for assistance with drug-drug interaction assessments. If additional support is needed, or for other information, prescribers can call the Ministry of Health’s COVID-19 antiviral support line for clinicians. The line is open Monday through Friday, 8:30 am to 4:30 pm and accessible at:

1-844-915-5005

When calling, be ready to provide patient information and a call-back number. A pharmacist will respond as soon as possible.

Most common drug-drug interactions in addition to those listed in contraindications include:

- Opioids such as fentanyl and methadone: Patients with substance use disorder who routinely use opioids should cautioned due to potential for overdose. Methamphetamine levels also increase; use caution.
- Transplant medications such as tacrolimus and cyclosporine: Transplant specialist consultation is recommended.
- Other statins such as atorvastatin: lipid lowering agents can be held for 5 days during co-administration with nirmatrelvir/ritonavir and restarted 3 days after treatment ends.
- Certain anticancer drugs, especially tyrosine kinase inhibitors (end in “-nib”): consult the BC Cancer Agency if an interacting anti-cancer drug is on the list or if the cancer medication is not on PharmaNet (IV medications).
- Some systemic and inhaled corticosteroids: Management depends on indication and type of steroid.
- Some antidepressants: Most can be co-administered, but patients need to be counselled about increased risk of adverse effects like sedation or dizziness.
- Calcium channel blockers like amlodipine, diltiazem or verapamil: lower doses can be co-administered with increased patient self-monitoring.
- HIV medications: Infectious Diseases consultation is recommended; the overall recommendation from BCCfE is to continue the regimen unaltered.
- Hormonal birth control: Back-up contraception methods should be used due to decreased levels of estrogen in estrogen-containing contraceptives.
For additional support on how to manage patients on anti-cancer medications or HIV patients, call:

**BC Cancer COVID Pharmacist:** bcc_covidpharmacist@bccancer.bc.ca; hours of coverage are Mon to Fri (8am - 4pm); emails sent on weekends and Statutory Holidays will be responded to by a pharmacist the following working day.

St. Paul's Hospital Ambulatory Pharmacy (HIV): 1-888-511-6222

**The RACE line** should not be used to obtain peer-peer consultation regarding prescribing practicalities but can be used for clinical consultation services in complex patients with COVID-19 who would benefit from Infectious Diseases expertise and input.

### 11. Pregnancy, Breastfeeding and Pediatrics

Currently available therapies have not been evaluated in pregnancy or breastfeeding. Most BC reproductive experts agree that remdesivir and, in rare occasions, sotrovimab may be used, and also support nirmatrelvir/ritonavir use due to lack of harm in animal studies and experience with other protease inhibitors in pregnant or breastfeeding women. Clinicians who are managing women who are candidates for treatment can connect with the Reproductive ID physician at **BC Women's Hospital (604-875-2161)** for guidance and assistance.

Most patients who are candidates for treatment are over the age of 50, and very few pregnant patients are expected to present for treatment. Such patients usually have other risk factors such as significant immunosuppression or cardiac issues and are followed by a specialist.

Patient 12-17 will only be offered treatment if they are significantly immunocompromised (i.e., CEV) and have additional risk factors as determined by consensus from their group. Such patients should be managed in collaboration with the BC Children’s Hospital Pediatric Infectious Diseases Specialist on-call (**BCCH Switchboard 604-875-2345**). Sotrovimab is the only approved therapeutic in this age group but due to its reduction in efficacy, remdesivir may be considered based on US labelling.

### 12. PAXLOVID Prescription

Nirmatrelvir/ritonavir (Paxlovid) is prescribed using a special prescription available [here on the BC Pharmacare webpage](#). E-from prescribing is also available for those registered.

It can be faxed to any pharmacy that stocks nirmatrelvir/ritonavir. For a list of pharmacies that carry Paxlovid kits, [click here](#).

### 13. Referring for Remesivir

Patients who are not candidates for nirmatrelvir/ritonavir due to drug-drug interactions or contraindications and are in the highest risk category (≥5%) need to be referred to the nearest Health Authority remdesivir infusion clinic. If remdesivir administration is not feasible, the clinic COVID doctor may discuss the possibility of sotrovimab with the patient under extenuating circumstances. Numbers are
current as of June 10, 2022.

- **Fraser Health Authority**: Directly order infusions. Forms are accessible on the FH Medical Staff website: JPOCSC Clinics & Services Forms -> Medical Day Care -> COVID-19 Therapy Pack. Fax to JPOCSC MDC 604-582-3742. If you need consultation, connect through RACE www.raceapp.ca Infectious Disease - COVID-19 Clinical. Requests will be returned by phone.

- **Vancouver Coastal and Providence Health**: Please make the referrals for remdesivir infusions through the CATe line at 1-888-COVID19

- **Interior Health Authority**: Contact the Interior Health COVID Therapeutics Virtual Clinica at 250-258-7369 or at COVIDTherapeutics@interiorhealth.ca

- **Island Health**: COVID-19 therapeutics clinic: 250-737-2030 (ext 44685) OR RJH ID on call

- **Northern Health**: 250-961-4936; this number will be answered 10:00am-10:00pm, 7 days a week

### 14. Provide Patient Information and Counselling

Use patient-specific materials to provide drug information.

**Patient information considerations:**

- **Patient-facing materials on nirmatrelvir/ritonavir (Paxlovid)** are located on the BCCDC website

- Provide clear drug-drug interaction management strategies. Ask patients to repeat instructions back. Call the patient’s pharmacy if significantly amending the patient’s medications. Follow-up by the dispensing pharmacist at the end of treatment may be useful if significant medication changes were made

- Provide any follow-up instructions, particularly if drug modifications have been made

- **Caution patients of common side effects.** For nirmatrelvir/ritonavir these can include:
  - Gastrointestinal upset, nausea, and diarrhea
  - Taste disturbance or altered taste sensation
  - Headache
  - Hypertension
  - Muscle aches

- Patients should be encouraged to call if they develop significant or unexpected adverse effects of these therapeutics. These are novel agents and real-world data on their use is currently lacking

- Adverse event reporting can be done through the Health Canada Adverse Drug reporting tool on their website

- **Use Practice Tool #4 – Counselling Checklist** if you are a pharmacist to ensure all patient information has been provided