BC COVID THERAPEUTICS COMMITTEE (CTC)

Practice Tool – Step-by Step Assessment Guide for Clinicians

GENERAL INFORMATION

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 – Drug-drug Interaction and Contraindication management tool

In this Tool you will find:

1. Who can prescribe and centralized prescribing through Health Link BC (811)
2. Who is recommended to receive antivirals including the patient self-screener
3. How to determine risk of hospitalization
4. Recommendations for treatment with antivirals
5. Tips for managing those in whom treatment is not recommended, and CanTreatCOVID trial
6. Confirming COVID-19 – Testing
7. Establishing symptoms and progression
8. Calculating treatment window
9. Assessing contraindications, including new dosing in end-stage renal disease
10. Assessing and managing drug-drug interactions
11. Peer-peer physician support including for pregnant women and pediatrics
12. PAXLOVID Prescription, supply and coverage
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

Physicians or nurse practitioners with a license to prescribe can prescribe nirmatrelvir/ritonavir.

While pharmacists can prescribed for certain conditions, COVID-19 is not part of the minor ailment list at this time, and pharmacists cannot prescribe nirmatrelvir/ritonavir or remdesivir.

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 Health Link 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.

Patients who call the office asking for an appointment for COVID-19 therapy can be first directed to the Self-Screener to see if treatment is recommended for them. 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 within the treatment window and take them through the basic recommendations for antivirals.

2. Who is Recommended to Receive Antivirals

Current treatment recommendations have been by the COVID Therapeutics Committee considering best-available evidence, the current risk of hospitalization form Omicron and the risk vs. benefit of treatment. These recommendations mirror those proposed by the Canadian Drug Agency (CADTH), but include a slightly broader group of patients who are not immunosuppressed. The CTC recommendations are approved by the Ministry of Health and are endorsed by the BCCDC.

It is *recommended* that the following patients receive treatment for mild-moderate COVID-19:

Patients who **test positive for SARS-COV-2**, with **appreciable symptoms** and a non-reassuring presentation and trajectory, who are at an **increased risk for hospitalization** or progression to severe COVID-19, such as:

- Individuals with **moderate to severe immunosuppression**, due to:
  - Solid organ transplant
  - Bone marrow or stem cell transplant
  - Treatment for a hematological malignancy
  - Receiving anti-CD-20 or B-cell depleting agents
  - Moderate-severe primary immunodeficiency
  - Receiving moderate immunosuppressive agents
  - Cancer treatment for solid tumors
  - Advanced or untreated HIV

- Individuals **≥60 years** who have **serious medical conditions**, who have been shown to significantly and consistently benefit from antivirals, such as those with:
    - End-stage renal disease (eGFR < 30ml/min or dialysis)
    - Diabetes treated with insulin
    - Severe or end-stage lung conditions such as COPD, asthma, interstitial lung disease, cystic fibrosis, or neurological conditions requiring Bi-Pap or ventilation
    - Severe intellectual or developmental disabilities
    - Rare blood and genetic disorders such as sickle cell disease, thalassemia, urea cycle defects

* Individuals **younger than 60 years** with a moderately immunosuppressive condition such as prostate or breast cancer or an immunological condition treated with a single moderately immunosuppressive drug have not been shown to routinely benefit from treatment with antivirals. Clinical judgement and consideration of other risk factors is strongly recommended.

What drugs cause severe immunosuppression?

- **Anti-CD-20 agents:** rituximab, ocrelizumab, ofatumumab, obinutuzumab, ibritumomab, tositumomab
- **B-cell depleting agents**: epratuzumab, MEDI-551, belimumab, BR3-Fc, AMG-623, Atacicept, antiBR3, alemtuzamab

What drugs cause moderate immunosuppression?

- **Biologics**: abatacept, adalimumab, anakinra, benralizumab, brodalumab, canakinumab, certolizumab, dupilumab, etanercept, golimumab, guselkumab, infliximab, interferon products (alpha, beta, and pegylated forms), ixekizumab, mepolizumab, natalizumab, omalizumab, resilizumab, risankizumab, sarilumab, secukinumab, tildrakizumab, tocilizumab, ustekinumab, or vedolizumab
- **Oral immune-suppressing drugs**: azathioprine, baricitinib, cyclophosphamide, cyclosporine, leflunomide, dimethyl fumerate, everolimus, fingolimod, mycophenolate, siponimod, sirolimus, tacrolimus, tofacitinib, upadacitinib, methotrexate, or teriflunomide
- **Oral steroids on an ongoing basis**: dexamethasone, hydrocortisone, methylprednisolone, or prednisone
- **Immune-suppressing infusions/injections**: cladribine, cyclophosphamide, glatiramer, methotrexate

What medical conditions warrant treatment in those aged 60 years and older?

- **End stage renal disease**: receiving dialysis (hemodialysis or peritoneal dialysis); stage 4 or 5 chronic kidney disease (eGFR <30ml/min); glomerulonephritis and receiving steroid treatment
- **Diabetes treated with insulin**: any regular prescription for daily insulin for the treatment of Type 1 or Type 2 diabetes
- **Severe or end-stage lung conditions**: cystic fibrosis, severe COPD leading to hospitalization because of COPD in the last year or on home oxygen treatment; evere asthma leading to hospitalization because of asthma in the last year or taking biologics for asthma; severe lung disease and at least one of the following: long-term home oxygen; assessment for a lung transplant; severe pulmonary arterial hypertension; severe pulmonary fibrosis/interstitial lung disease

- **Neurological conditions requiring respiratory support**: Neurological or other conditions causing significant muscle weakness around lungs requiring the use of a ventilator of continuous Bi-level positive airway pressure (Bi-PAP)
- **Severe intellectual or developmental disabilities**: Down Syndrome, Cerebral Palsy, or Intellectual Developmental Disability (IDD), or receiving supports from Community Supports for Independent Living (CSIL) or Community Living British Columbia (CLBC) or currently receiving supports or assessed and eligible for CLBC supports or Nursing Support Services program
- **Rare blood disorders**: homozygous sickle cell disease, highest risk thalassemia, atypical Hemolytic Uremic Syndrome or Paroxysmal Nocturnal Hemoglobinuria
- **Rare genetic metabolic disorders**: certain metabolically unstable inborn errors of metabolism: urea cycle defects; methylmalonic aciduria; propionic aciduria; glutaric aciduria; maple syrup urine disease

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 antivirals are recommended based on the above.

The recommendations have been developed after a thorough analysis of the best available literature, including an evaluation of the efficacy of Nirmatlervir/ritonavir in BC. This is 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.

3. What is the Risk of Hospitalization and Expected Benefit

Risk of Hospitalization in the Current Pandemic Context

Knowing the absolute risk of hospitalization from COVID-19 can help with clinical decision making and discussions with patients, especially when antivirals are not recommended.

In the BC population, the BCCDC found that the general risk of hospitalization and mortality from the first-ever COVID-19 infection is approximately 0.3% and 0.1% respectively, making treatment futile for the average individual with COVID-19. This risk approaches zero in those younger than 60 and is slightly higher in the elderly. This risk is likely even lower now because most patients have had COVID-19 and have strongly protective hybrid immunity. Nearly 90% of BC residents have also received at least one dose of the Omicron XBB mRNA vaccine which continues to offer excellent protection from hospitalization and death from the currently circulating variants of concern.

Despite this low risk, recent BC-specific evidence has suggests that the risk of hospitalization is higher in those who are immunocompromised and have certain high-risk conditions. A published BC analysis of nirmatrelvir/ritonavir during the Omicron waves showed that untreated patients who are severely immunocompromised, moderately immunosuppressed and have certain high risk conditions had a risk of hospitalization and mortality of 3.2%, 3.1% and 3.5%, respectively. It is important to highlight that with the exception of severely immunosuppressed, nearly all of the hospitalization events occurred in those 60 years or older, with younger individuals experiencing an event rate below 1%.

Expected Benefit

Initially, randomized controlled trials of therapies for mildly-moderately ill patients showed a decrease in risk from ~5% to ~1% with treatment, for an NNT of 25 to prevent one hospitalization. However, real-world data have shown that the benefit is likely much smaller, with an average NNT of 100-200 to prevent one hospitalization. As hospitalization rates do not generally drop below 1% even in treated patients, treatment likely has no benefit in individuals with a baseline hospitalization risk of below 1%. In the BC analysis above where nirmatrelvir/ritonavir was beneficial, the NNT was between 30 and 60. This NNT was calculated in the groups of patients mentioned in the recommendations herein and informs this guide.

4. What Antiviral to Prescribe

Nirmatrelvir/ritonavir (Paxlovid) is the only oral antiviral for SARS-COV-2 currently available in Canada. Nine of 10 patients in whom treatment is recommended can safely be prescribed nirmatrelvir/ritonavir. Non-antiviral therapies such as monoclonal antibodies have become obsolete due to resistance; however this remains to be an active area of drug development. Other reproposed therapies such as inhaled corticosteroids are not recommended.

Nirmatrelvir/ritonavir is recommended within 5 days^ of symptom onset for patients with appreciable symptoms and a non-reassuring presentation and trajectory who are at an increased risk for hospitalization or progression to severe COVID-19 due to conditions or medication above.

Recommended dosing guidance for nirmatrelvir/ritonavir based on renal function:

Last available eGFR (ml/min)	Dosing schedule
60 or above	Nirmatrelvir/ritonavir **300/100mg PO BID** x 5 days
30 to 59	Nirmatrelvir/ritonavir **150/100mg PO BID** x 5 days
Less than 30 (no dialysis)	Nirmatrelvir/ritonavir **300/100mg PO once daily on day 1, then 150/100mg PO once daily** on days 2-5 (Pharmacist will dispense regular nirmatrelvir/ritonavir kits and remove all PM doses of 300/100mg as well as one tablet of nirmatrelvir 150mg from the AM dose on days 2-5)
Dialysis	Nirmatrelvir/ritonavir **300/100mg PO once daily on day 1, then 150/100mg PO once daily** on days 2-5, given after dialysis on dialysis days (Pharmacist will dispense regular nirmatrelvir/ritonavir kits and remove all PM doses of 300/100mg as well as one tablet of nirmatrelvir 150mg from the AM dose on days 2-5)

NOTES:

^The symptom window for nirmatrelvir/ritonavir can be extended to 7 days in outpatients if they would otherwise be referred for remdesivir solely based on its longer treatment window.

Remdesivir is recommended within 7 days of symptom onset as an alternative to nirmatrelvir/ritonavir if nirmatrelvir/ritonavir cannot be given due to drug-drug interactions or contraindications (*See Practice Tool – Drug Interactions and Contraindications*).

Recommended dosing guidance for remdesivir based on renal function:

Most recent eGFR (ml/min)	Dosing schedule
30 or above	Remdesivir **200mg IV once daily** on day 1, followed by **100mg IV once daily** on days 2 and 3
Less than 30 (no dialysis)	Remdesivir **200mg IV once daily** on day 1, followed by **100mg IV once**, 48 hours later
Dialysis	Remdesivir **200mg IV once daily** on day 1 post-dialysis, followed by **100mg IV once** post dialysis, 48-72 hours later

NOTES:

The decision to offer remdesivir vs. off-label nirmatrelvir/ritonavir in those with eGFR <30ml/min or drug-drug interactions should be based on joint decision making between the patient and clinician in consideration of risk vs. benefit of either drug and individual patient factors.

Inpatients with mild-moderate COVID-19 who are at increased risk of progression to severe disease due to conditions or medications above may be offered nirmatrelvir/ritonavir or remdesivir based on contraindication, drug-drug interactions, IV access and planned length of stay. Patients should complete the antiviral started as there are no data to guide switching between antivirals midway through the treatment course.

5. Managing those in Whom Treatment is NOT Recommended

The biggest challenge faced by primary care physicians, nurse practitioners, emergency department physicians and community pharmacists is counselling patients who expect antiviral treatment but in whom treatment is not expected to be beneficial. Strategies used by clinicians to support antimicrobial stewardship (for example not prescribing antibiotics for otitis media) can be employed to have honest and informed conversations with patients.

The following tips can be used when discussing antiviral treatment with patients:

- Inform patients that their absolute risk of hospitalization is below a percentage point and that antivirals cannot reduced that any further
- Dispel misinformation such as that nirmatrelvir/ritonavir saves lives, makes people feel better faster or prevents post-COVID condition (Long COVID)
- Share scientific resources such as the recent Therapeutics Initiative letter that reiterates these points
- Educate patients that the risk of a side-effect such as nausea, vomiting and taste disturbances is ~25%. In BC, about one in 10 patients does not finish prescribed treatment or discontinues it due to side effects
- If drug-drug interactions with ritonavir are present, counsel patient on the risk vs. benefit of starting antivirals

- Reassure patients with mild cold symptoms that the risk of progression to severe disease is about the same as with any other virus that causes respiratory illness in the community
- Use the "Watchful Waiting" approach: ask those with mild symptoms to self-monitor, reiterating that there is a 5-day treatment window and treatment may be initiated if they worsen
- Ask patients to recall what happened when they had COVID in the past. If they have recovered, reassure them that they will likely recover again and now have stronger hybrid immunity
- Discuss the importance of vaccination (both for COVID-19 and influenza) and assure patients that the "match" against currently circulating variants is excellent
- Use the opportunity to motivate patients to manage or prevent chronic conditions appropriately in order to further reduce their chance of severe disease
- Some patients respond to cost information and want to contribute to a cost-effective health care system. In such cases, share that nirmatrelvir/ritonavir costs $1,500 a course and not prescribing it when there is no benefit helps fight the ballooning costs of health care
- Acknowledge the impact of direct-to-consumer advertising by the manufacturer of nirmatrelvir/ritonavir and inform patients that such advertising is intended to evoke emotions to sell a product and not provide scientific information

As the benefit of antivirals in most patients mild-moderate COVID-19 in the current state of the pandemic is still unknown, a randomized controlled trial designed to answer this question is ongoing in BC. This trial is called CanTreatCOVID and patients can easily self-enrol on line or by phone.

CanTreatCOVID is open to:

- Any adult who tested positive for COVID-19 in the last 5 days AND
- Is 50 years of age and older OR
- Has a chronic medical condition

Patients will be screened, randomized to treatment or standard of care if they consent to participate, receive medication (if randomized to treatment) in the mail and be contacted for follow-up by phone. There are no in-person visits required.

Patients can enrol **on-line at the CanTreatCOVID website** or by phone at **1-888-888-3308.**

6. 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 especially with repeat testing.

Federally obtained RATs which are free of charge to patients continue to be available in BC. 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.

High risk patients that present for care of respiratory symptoms without a diagnosis are recommended to have a laboratory-based PCR test. PCR is much more sensitive and differentiates from other circulating pathogens such as influenza and respiratory syncytial virus (RSV). Detailed testing guidance for RAT and PCR (NAAT) in primary care are available here.

7. 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 or have a non-reassuring clinical presentation or trajectory.**

A non-reassuring clinical presentation is one that poses concern to the health care provider. A patient with an active haematological malignancy on treartment may only have a low-grade fever; however, this may not be reassuring to their transplant team.

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 upper respiratory symptoms and no lower respiratory or systemic symptoms. Patients can have various signs and symptoms of COVID-19 (e.g., low-grade fever, cough, sore throat, malaise, headache, 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 and high-grade fever 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.*

8. Calculate the Time since Symptom Onset

Symptom windows vary with each therapeutic agent and generally follow study inclusion criteria. **Remdesivir 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 patients for whom antiviral treatment is recommended, 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 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.*

9. Assess Contraindications

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

Most common contraindications with nirmatrelvir/ritonavir include:

- 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:
    - **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)

If eGFR or renal function available:	
eGFR ≥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 ≥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.

- **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 Palxovid treatment and 2 additional days). This option may be used if switching to dabigatran is not feasible.
- **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
- **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
- **Some antipsychotics** like clozapine that are hard to adjust, or injectable quetiapine
- **Inhaled salmeterol;** holding salmeterol during a respiratory illness may not be possible but an alternative inhaler (e.g., salbutamol) could be considered
- **Antiepileptics** such as carbamazepine and phenytoin are contraindicated and due to prolonged enzyme induction, there are no modification options
- **Opioids especially fentanyl;** patients who use drugs need to be very carefully selected based on the risk of overdose, counselled and monitored

A note on renal disease: Canadian nirmatrelvir/ritonavir labelling does not recommend administration in end-stage renal disease (eGFR <30ml/min) or dialysis. However, as per feedback from consultation with BC nephrology experts and careful review of the literature, nirmatrelvir/ritonavir may be used with renal dose adjustments. This strategy has also been approved in other jurisdictions. Patients without known renal disease can be prescribed full-dose nirmatrelvir/ritonavir without ordering baseline creatinine, and in those with reduced renal function, the most recent SCr can guide treatment decisions. Boarder-line eGFR (e.g., 28ml/min) should be assessed using clinical judgment; little risk exists by choosing either dosing.

The following nirmatrelvir/ritonavir dosing has been developed in collaboration with nephrology experts:

Last available eGFR (ml/min)	Dosing schedule
60 or above	Nirmatrelvir/ritonavir **300/100mg PO BID** x 5 days
30 to 59	Nirmatrelvir/ritonavir **150/100mg PO BID** x 5 days
Less than 30 (no dialysis)	Nirmatrelvir/ritonavir **300/100mg PO once daily on day 1, then 150/100mg PO once daily** on days 2-5

	(Pharmacist will dispense regular nirmatrelvir/ritonavir kits and remove all PM doses of 300/100mg as well as one tablet of nirmatrelvir 150mg from the AM dose on days 2-5)
Dialysis	Nirmatrelvir/ritonavir **300/100mg PO once daily on day 1, then 150/100mg PO once daily** on days 2-5, given after dialysis on dialysis days (Pharmacist will dispense regular nirmatrelvir/ritonavir kits and remove all PM doses of 300/100mg as well as one tablet of nirmatrelvir 150mg from the AM dose on days 2-5)

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.

10. Assess/Manage Drug-Drug Interactions (pertains to nirmatrelvir/ritonavir)

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 – 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.

If you need DDI support, community pharmacists who dispense Paxlovid can help. Please contact the community pharmacy that will dispense Paxlovid for the patient for assistance with drug-drug interactions. If drug interactions are found at the time of dispensing, be prepared that the assessing pharmacist will contact you to put a management plan in place.

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: Regional BC Cancer Centre pharmacists are available to answer questions between the hours of 8am - 4pm Monday through Friday; emails sent on weekends and Statutory Holidays will be responded to by a pharmacist the following working day. Refer to the table below for contacting the correct centre:

Centre	Pharmacist Consult Line
Abbotsford	Email: _bcca_acacupharmacists@bccancer.bc.ca Phone: 604-851-4710 EXT. 645242
Kelowna	Email: _BCCA_CSIPharmacists@phsa.ca Phone: 250-712-3900 ext 686758
Prince George	Email: cndan@bccancer.bc.ca Phone: 250-645-7317
Surrey	Email: _BCCA_FVCCPharmacists@phsa.ca> Phone: 604-930-4002 #2
Vancouver	Email: ACUPharmacist@phsa.ca Phone: 604- 877-6098 ext 672632
Victoria	Email: VICACUPharm@bccancer.bc.ca Phone: 250-519-5500 ext 693795

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

The RACE line should not be used to obtain peer-peer consultation regrading prescribing practicalities but can be used for clinical consultation services by prescribers 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 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 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).** A decision to give nirmatrelvir/ritonavir in this age group based on US labelling may be made; otherwise prescribers can order remdesivir as per the Canadian product monograph.

12. PAXLOVID Prescription, Supply and Coverage

Writing a prescription for nirmatrelvir/ritonavir (Paxlovid) using the Paxlovid Prescription Form is recommended. The prescription for is available here on the BC Pharmacare webpage. E-from prescribing is also in place for those registered. The form is not mandatory, but it guides prescribers through the various steps much like a pre-printed order set. There are no other administrative actions required to prescribe nirmatrelvir/ritonavir.

As of May 23, 2024, BC will stop using the federally procured supply of nirmatrelvir/ritonavir as these supplies are sparse and expire on May 31, 2024. From that point, any pharmacy will be able to order kits of nirmatrelvir/ritonavir from their regular suppliers and fill prescriptions for nirmatrelvir/ritonavir using standard processes for any other Schedule 1 prescription medication.

There are currently no known shortages or backorders of nirmatrelvir/ritonavir. All pharmacies are expected to be able to fill a nirmatrelvir/ritonavir prescription within a reasonable time frame.

The Ministry will release information about the coverage of nirmatrelvir/ritonavir by Pharmacare on their website on May 23, 2024. Nirmatrelvir/ritonavir coverage will also be searchable using the BC Pharmacare Formulary search. The Pharmacare newsletter will also be sent out to alert pharmacists and clinicians about the listing decision.

13. Referring for Remdesivir

Patients who are not candidates for nirmatrelvir/ritonavir due to drug-drug interactions or contraindications can be referred to the nearest Health Authority remdesivir infusion clinic. Numbers are current as of June 10, 2023.

- **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 Clinic 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:** CATe physician to consult the NH Remdesivir referral document as phone numbers and processes vary by site

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 – Counselling Checklist if you are a pharmacist to ensure all patient information has been provided