Ontario Health Recommendations for Outpatient Use of Intravenous Remdesivir (Veklury) in Adults

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This document was developed by Ontario Health's Infectious Diseases Advisory Committee based on best available evidence and expert consensus. There are limitations to the evidence that is currently available. **Prescribers must determine whether adopting suggested information is clinically appropriate for individual patients through a comprehensive risk-benefit assessment.**

Purpose

The objective of this document is to provide recommendations to guide clinicians on appropriate prescribing of intravenous (IV) remdesivir to adults (≥ 18 years) who can receive treatment in an **outpatient setting** (e.g., community nursing clinic) for coronavirus disease 2019 (COVID-19).

Evidence Summary for the Outpatient Use of Remdesivir

Evidence to support outpatient IV remdesivir treatment is largely based on a single randomized, double-blind, placebo-controlled trial (PINETREE) in unvaccinated, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive, high-risk patients (n=562) who had symptom onset within the previous **seven** days, at least one risk factor for disease progression or age ≥ 60 years (regardless of other factors). Patients were randomized to receive a 3-day course of IV remdesivir (n= 279) or placebo (n=283). The most common underlying conditions were diabetes mellitus, obesity, and hypertension. The risk of COVID-19–related hospitalization or death from any cause by day 28 was 87% lower in the remdesivir group than in the placebo group (HR: 0.13; 95% CI, 0.03 to 0.59; P = 0.008). Remdesivir was well tolerated with mild nausea, headache, and cough being the most common side effects. [1] A subsequent sub-group analysis in 2023 evaluated the efficacy of remdesivir by time from symptom to treatment initiation and by the number of baseline risk factors. Efficacy was maintained for patients starting at > 5 days from symptom onset and for treating patients with low numbers (≤ 2) or high number of risk factors (≥ 3) for severe COVID-19). [2]

The data from the PINETREE study is limited because several high-risk groups were underrepresented (e.g., only 5% of study patients were immunocompromised), the study population was unvaccinated, and it was conducted prior to the emergence of Omicron and its sub-variants. Subsequent prospective, observational and retrospective real-world studies have evaluated outpatient remdesivir in these underrepresented high-risk groups, in the setting of high vaccination rates, and since the emergence of Omicron. Overall, these studies varied in their definitions of "high risk", and hospitalization rates and deaths with the use of remdesivir varied between studies. However, since the emergence of Omicron and its sub-variants, evidence has accumulated to demonstrate that remdesivir is safe and effective for outpatient treatment of COVID-19

in vaccinated patients.[3–10] Remdesivir also appears to be clinically comparable to nirmatrelvir/ritonavir in a vaccinated population with at least one risk factor for severe COVID-19 during Omicron.[5,6]

Immunocompromised individuals may have diminished responses to COVID-19 vaccines and are also at higher risk for prolonged infections and complications from SARS-CoV-2 infection.[11] For immunocompromised patients, data from retrospective and prospective studies demonstrated that remdesivir reduced the risk of hospitalization or death, even in the setting of high vaccination rates and Omicron.[4,7,9,10,12,13] These studies included patients with solid organ transplant, hematologic malignancies, hematopoietic stem cell transplants, and autoimmune diseases.

Additional studies have described models of administering IV remdesivir in the outpatient setting. They have demonstrated that outpatient administration (including at-home administration) is feasible and safe.[14–16]

Recommendations

In Canada, both intravenously administered remdesivir (Veklury®) and orally administered nirmatrelvir/ritonavir (Paxlovid®) are Health Canada approved therapies for treatment of non-hospitalized patients with mild to moderate COVID-19 with a high risk of progression to severe COVID-19 *(see **Table 1**).* Randomized and observational evidence demonstrates that both these therapies can reduce hospitalizations and death. To date, there are no randomized controlled studies that directly compare these two therapies. In general, choice of anti-viral therapy is based on patient-specific factors (e.g., medical contraindications, significant drug-drug interactions), time from symptom onset, availability of the therapy, and feasibility of administration.[17–19]

The following consensus-based recommendations were informed by evidence retrieved from a systematic literature search conducted in May 2023 and available Canadian/international guidelines.[17–32] Considering the best available evidence and health system factors, the Committee made the following recommendations *(See **Figure 1** for a suggested treatment algorithm*):

1. **Patients must be at high risk for hospitalization or death due to COVID-19.**
   Antivirals (nirmatrelvir/ritonavir **or** remdesivir) are indicated in outpatients with mild to moderate COVID-19 symptoms who are at **high risk** of hospitalization or death due to COVID-19. *(See section on identification of high-risk patients below).* Mild-to-moderate respiratory illness includes fever and one or more clinical findings of lower respiratory illness (e.g., cough, shortness of breath, and breathing difficulties).[31]

2. **A COVID-19 diagnosis is required prior to initiating antiviral therapy.**
   Patients must have COVID-19 symptoms and a positive test for SARS-CoV-2 based on PCR, rapid molecular, or rapid antigen test to be considered for outpatient nirmatrelvir/ritonavir or remdesivir therapy.

3. **Nirmatrelvir/ritonavir is the preferred first-line therapy when safe and feasible.**
   Nirmatrelvir/ritonavir is the **preferred** outpatient therapy for treating patients with *mild to moderate* COVID-19 who are at **high risk** of severe COVID-19, regardless of vaccination status or prior COVID-19 infection due to the feasibility of administration:
   - Therapy must be initiated within **5 days** of symptoms onset.
   - Nirmatrelvir/ritonavir tablets can be crushed. A feeding tube is not an absolute contraindication to use. [33,34]
   - For patients with renal impairment or on dialysis, doses can be adjusted.
   - **Assess for drug-drug interactions. Prior to considering remdesivir, ensure that drug-drug interactions with nirmatrelvir/ritonavir cannot be safely mitigated.** Mitigating strategies include dose reductions and/or short-term treatment interruption. Consult with specialists as required (e.g., oncology, transplant). Consultation with a pharmacist who can obtain a complete medication, recreational, and natural health product history from the patient is recommended. *(See Table 1 for suggested resources).*

4. **Remdesivir is indicated where nirmatrelvir/ritonavir is contraindicated (e.g., drug-drug interaction that cannot be safely managed, medical contraindication) or when patients are beyond the treatment window for nirmatrelvir/ritonavir initiation (i.e., symptom onset > 5 days).**
   - Initiation of therapy within 7 days of symptom onset is recommended.
     (Given the lack of evidence, initiation beyond this date should only be considered based on clinical judgement.)
   - Patients need to be able to receive **three days of consecutive IV** therapy (Consider travel requirements or other delivery barriers that may exist).
   - The use of beta-blockers is not a contraindication to using remdesivir. *(See Table 1)*

Guidance for Identifying Patients at High Risk for Severe COVID-19

Defining a high-risk population is challenged by the evolving nature of the SARS-CoV-2 virus. Evidence continues to emerge to inform risk assessments. In general, older age is the strongest risk factor for severe outcomes due to COVID-19.[20] Other risk factors include being immunocompromised, unvaccinated or under vaccinated, or having one or more underlying medical conditions.[17,20,27] Patients with multiple risk factors have a higher risk of severe COVID-19, and are most appropriate for antiviral therapy.

"High-risk" patients who may be considered for antiviral therapy include:

1. **Adults ≥ 60 years of age, regardless of vaccination status, with no other risk factors.**

2. **Adults who are immunocompromised, regardless of age, vaccine status, or prior infections.**
   e.g., active hematological malignancy or post stem cell transplant or CAR T-cell therapy in last 6 months, solid organ transplant, hypogammaglobulinemia, taking prednisone >20 mg/day (or equivalent) for more than 14 days, or other moderately or severely immunosuppressive therapies (e.g., anti-CD20 agents, alkylating agents, cancer chemotherapy),

3. **Adults with inadequate immunity**, i.e.,
    - Unvaccinated or under-vaccinated *(e.g., completed primary series AND last COVID-19 vaccine dose was more than 6 months ago AND last SARS-CoV-2 infection was more than 6 months ago)*
        - See the most recent immunization guidance from National Advisory Committee on Immunization to determine if your patient is under-vaccinated

4. **Adults with one or more underlying conditions that puts them at high risk for severe COVID-19 outcomes.**
   The US Centers for Disease Control and Prevention maintains an evidence-informed list of underlying medical conditions associated with severe COVID-19.[20] Based on the current list, the Committee highlighted the following high-risk medical conditions:

    - Cerebrovascular disease
    - Chronic kidney disease – including people receiving dialysis
    - Chronic lung diseases limited to: Asthma, Bronchiectasis, COPD (Chronic obstructive pulmonary disease), Interstitial lung disease, Pulmonary embolism, Pulmonary hypertension
    - Chronic liver diseases limited to: Cirrhosis, Non-alcoholic fatty liver disease, Alcoholic liver disease, Autoimmune hepatitis
    - Cystic fibrosis
    - Diabetes mellitus (type 1 and 2)
    - Disabilities and developmental delay, including Down syndrome
    - Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
    - Mental health conditions limited to: Mood disorders (including depression), Schizophrenia spectrum disorders
    - Neurologic conditions that cause an inability to control respiratory secretions or to communicate disease progression. e.g., cognitive disorders such as Alzheimer's type dementia
    - Obesity (BMI >30 kg/m^2 or >95th percentile in children)
    - Pregnancy and recent pregnancy (42 days post-partum/end of pregnancy)
    - Smoking, current and former
    - Tuberculosis

Individuals who are at a higher risk of poor outcomes from COVID-19 based on social determinants of health should be considered priority populations for access to antivirals. Individuals with certain medical or social vulnerabilities may experience challenges in recognizing, communicating or acting on progressing COVID-19 symptoms.[35] Individuals at higher risk include Indigenous people, Black people, other members of racialized communities people who are underhoused, individuals with intellectual, developmental, or cognitive disability, people who use substances regularly (e.g., alcohol) and/or live with mental health conditions. [20,35–42]

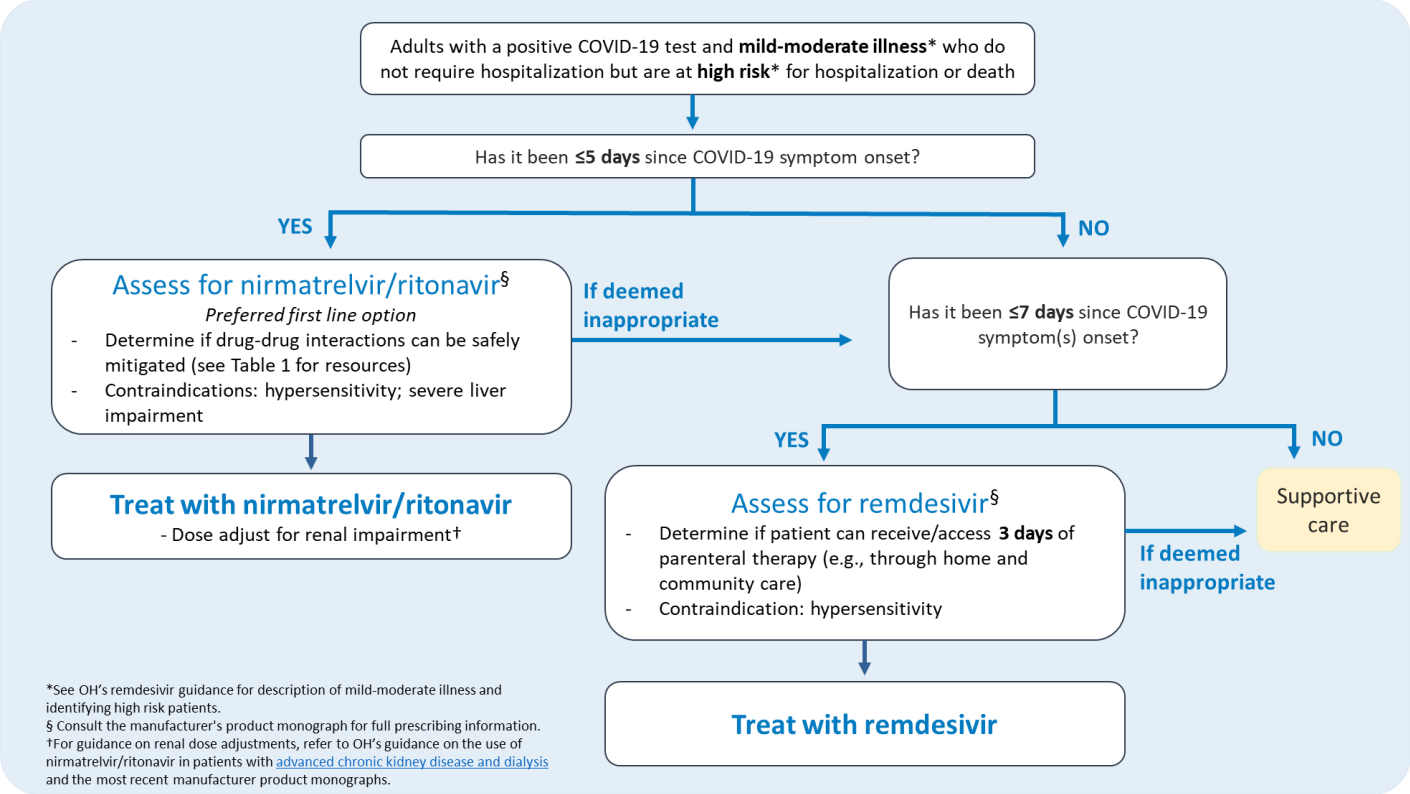
Table 1: Overview of recommended therapies for mild to moderate COVID-19

	Nirmatrelvir/Ritonavir (Paxlovid)	Remdesivir (Veklury)
Place in Therapy	Preferred first line therapy	Alternative to nirmatrelvir/ritonavir
Indication(s) ***(Health Canada approved)***	Treatment of mild-to-moderate COVID-19in *adult*s with positive results of direct SARS-CoV-2viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. [43]	• Hospitalized adults and adolescents (aged 12 years to less than 18 years who weigh at least 40 kg) with pneumonia requiring supplemental oxygen. • *Non-hospitalized adults and pediatric patients (weighing at least 40 kg)* with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. [44]
Prescribing Window	Initiate within 5 days of symptom onset [43]	Initiate within 7 days of symptom onset. [44]
Usual Dose ***(mild-moderate COVID-19)***	300 mg nirmatrelvir + 100 mg ritonavir Both taken together orally twice daily for **5 days** [43]	Adults and pediatrics weighing ≥40 kg: [44] • Loading dose: 200 mg IV on **day 1** • 100 mg IV on **day 2** and **day 3**
Dosing in renal impairment*	**GFR 30 mL/min - 60 mL/min:** 150 mg nirmatrelvir + 100 mg ritonavir both twice a day for 5 days. **GFR <30 mL/min**: 300 mg nirmatrelvir + 100 mg ritonavir both on **day 1** then 150 mg nirmatrelvir + 100 mg ritonavir both once a day for 4 more days. [45,46]	No dose adjustment required with impaired renal function, including patients on dialysis. [47]

	Nirmatrelvir/Ritonavir (Paxlovid)	Remdesivir (Veklury)
Potential for Drug Interactions	Nirmatrelvir/ritonavir are major substrates of CYP3A4. Ritonavir is a potent inhibitor of CYP3A4. [48] **Resources:** **Liverpool's COVID-19 Interaction Checker** (link) **University of Waterloo/University of Toronto: Nirmatrelvir/Ritonavir (Paxlovid) – What Prescribers and Pharmacists Need to Know** (link) **SHS + UHN - Paxlovid-Oncology DDI** (link)	Minor substrate of CYP2D6, CYP3A4.[48] Few clinically significant drug interactions
Administration considerations	Nirmatrelvir and ritonavir are film-coated tablets that can be crushed and administered through feeding tubes if necessary. [33]	Remdesivir is only available as an IV formulation which requires nursing support to administer on three consecutive days.
Clinically relevant Contraindications	Hypersensitivity Severe Hepatic impairment (Child-Pugh C) [43]	Hypersensitivity Sinus bradycardia is a precaution but not a contraindication. [44]

* Dosing recommendations may differ from Health Canada recommended approved dosing.

Figure 1: Treatment Algorithm for non-hospitalized adults with COVID-19



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Additional resources

Visit the Ontario Health COVID-19 treatment website for the latest resources on remdesivir and other COVID-19 therapeutics, including information about how to access COVID-19 therapeutics (nirmatrelvir/ritonavir and remdesivir) for patients in the community.

For guidance on COVID-19 screening, testing visit the Ministry of Health's COVID-19 website on Guidance for the Health Sector.

Questions?

For any questions on the contents of this document, please contact the Provincial Drug Reimbursement Programs (PDRP) at OH-CCO_InfoPDRP@ontariohealth.ca.

Need this information in an accessible format? 1-877-280-8538, TTY 1-800-855-0511, info@ontariohealth.ca.

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Notes: Each member of the Infectious Diseases Advisory Committee was asked to declare any actual, potential, or perceived conflicts of interest.

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