Recommendations for Antiviral Therapy for Adults with Mild to Moderate COVID-19

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This document was developed by Ontario Health's Infectious Diseases Advisory Committee (IDAC) based on best available evidence and expert consensus. There are limitations to the evidence that is currently available. **Prescribers should conduct a comprehensive risk-benefit analysis when applying the recommendations to inform individualized treatment decisions.**

Introduction

This document is intended to provide recommendations on the appropriate prescribing of oral nirmatrelvir/ritonavir (Paxlovid) and intravenous (IV) remdesivir (Veklury) for adults 18 years and older for the treatment of mild to moderate coronavirus disease 2019 (COVID-19).

The severity classification for mild, moderate and severe COVID-19 has been revised to better align with definitions commonly used by other Canadian and international health authorities and guidelines. The risk factors associated with more severe COVID-19 outcomes where antiviral therapy is recommended have also been revised to reflect the changes in SARS-CoV-2 pathogenicity from circulating strains in the community and pre-existing immunity derived from prior infection or vaccination. The generalizability of the landmark clinical trials for remdesivir and nirmatrelvir/ritonavir to current clinical practice is limited because they were conducted prior to the emergence of Omicron SARS-CoV-2 variant in people who were unvaccinated or had not developed immunity from a prior COVID-19 infection.

This guidance document will be updated as new relevant information becomes available.

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COVID-19 Severity Classification

Classification of illness severity varies among different references and health authorities. ***Table 1*** outlines the updated classification of disease severity in Ontario developed by the Committee following consensus-based recommendations and adaptation from Canadian and international guidelines.[1–7] ***Table 2*** describes the common, less frequent and rare symptoms reported by individuals with COVID-19 during the Omicron era.[8,9]

In the early stages of illness, COVID-19 is commonly associated with symptoms such as runny nose, sneezing, sore throat and headache.[8] Disease progression can lead to lung inflammation with shortness of breath and hypoxia, followed by hyperinflammation characterized by acute respiratory distress syndrome, systemic inflammatory response syndrome, septic shock, coagulation disorders or cardiac failure.[10] Severe COVID-19 is associated with an increased risk of death.[10]

Table 1: COVID-19 Severity Classification

COVID-19 Severity	Definition
Mild	Individuals who have: 1. Any of the signs and symptoms of COVID-19 (**Table 2**) **AND** 2. Oxygen saturation (SpO_2) greater than 92% at rest without supplemental oxygen or no increase in supplemental oxygen from baseline
Moderate	Individuals who have: 1. SpO_2 greater than 92% at rest without supplemental oxygen or no increase in supplemental oxygen from baseline **AND** 2. Evidence of lower respiratory disease during clinical assessment or imaging
Severe	Individuals who **newly require supplemental oxygen OR** Individuals who require an **increase in supplemental oxygen** from baseline, with or without worsening or progressive signs and symptoms of COVID-19
Critical	Individuals who require any **new respiratory support** (i.e., high-flow oxygen, non-invasive ventilation, mechanical ventilation) and/or vasopressor/inotropic support

Table 2: Symptoms Associated with COVID-19 During the Omicron Era

Frequency of Symptoms[8,9]	Symptoms[8,9]
Common symptoms (Reported by greater than 50% of individuals)	• Headache • Runny nose • Sneezing • Sore throat
Less frequent symptoms (Reported by 10% to 50% of individuals)	• Chills • Dizziness • Fever • Gastrointestinal symptoms (e.g., nausea, diarrhea, abdominal pain) • Hoarse voice • Joint pain • Muscle pain • New loss of or altered sense of smell • Persistent cough
Rare symptoms (Reported by less than 10% of individuals)	• Chest pain • Confusion/brain fog • Delirium • Irregular heartbeat • Skin changes • Shortness of breath • Swollen glands

Overview of Treatment for Mild to Moderate COVID-19

The goals of treatment in patients with mild to moderate COVID-19 are to prevent:

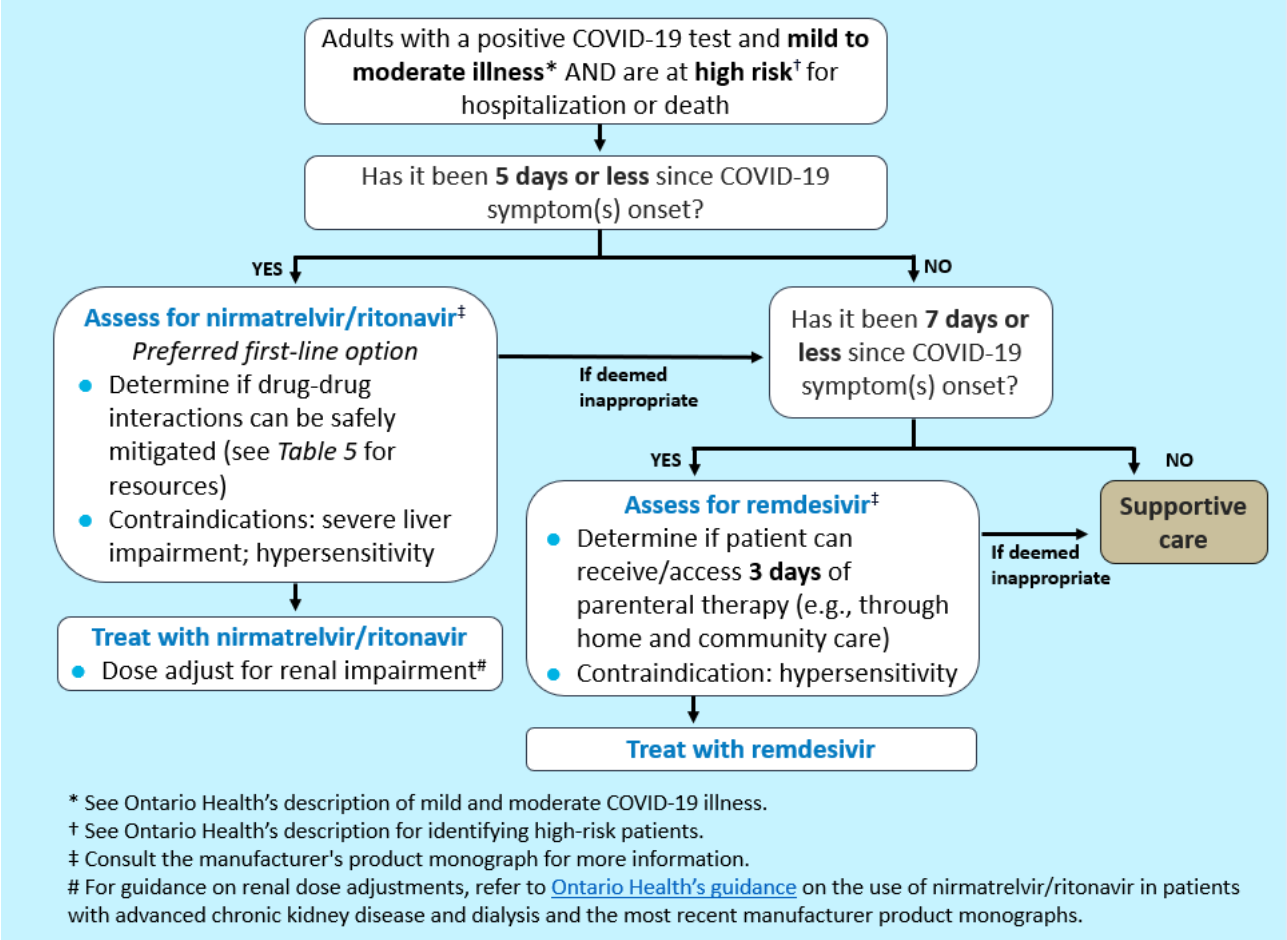
- Progression to severe disease
- The need for supplemental oxygen
- Emergency department visits
- Hospitalization
- Death

The following consensus-based recommendations are informed by best available evidence retrieved from a systematic literature search conducted between November and December 2023, Canadian and international guidelines, and health system considerations. The Committee's recommendations are applicable to:

1. Non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease, including patients presenting to the emergency department or residents of long-term care homes, retirement homes and other congregate living settings **OR**
2. Hospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease, including nosocomial COVID-19 or patients admitted for reasons other than COVID-19 but have symptomatic mild to moderate COVID-19

See ***Figure 1*** for a suggested treatment algorithm.

Figure 1: Treatment Algorithm for Mild to Moderate COVID-19



* See Ontario Health's description of mild and moderate COVID-19 illness.
† See Ontario Health's description for identifying high-risk patients.
‡ Consult the manufacturer's product monograph for more information.
# For guidance on renal dose adjustments, refer to Ontario Health's guidance on the use of nirmatrelvir/ritonavir in patients with advanced chronic kidney disease and dialysis and the most recent manufacturer product monographs.

Recommendations for Antiviral Therapy Selection

1. **A microbiologically-determined COVID-19 diagnosis is required prior to initiating antiviral therapy.**
   Patients must have COVID-19 symptoms and a positive test based on polymerase chain reaction (PCR), rapid molecular or rapid antigen test to be eligible for nirmatrelvir/ritonavir or remdesivir.

2. **Patients must be at high risk of hospitalization or death due to COVID-19.**
   Antiviral therapy with nirmatrelvir/ritonavir or remdesivir is indicated in patients with mild to moderate COVID-19 symptoms who are at high risk of hospitalization or death. High-risk patients are prioritized for treatment because clinical studies have demonstrated the greatest benefit (e.g., significantly reduced risk of emergency department visits, need for supplemental oxygen, COVID-19-related hospitalization, death) in this patient population.[11–14] Similar benefits have not been reported in patients with low or moderate risk of progression to severe disease.[15] Antiviral treatment is not recommended for asymptomatic patients with COVID-19.[3]

Reliable risk prognostication models for hospitalization and other important outcomes for patients with non-severe COVID-19 remain limited.[16] Risk factors associated with more severe COVID-19 outcomes may evolve over time due to the circulation of new variants and in the context of immunity from natural infection and vaccination. Treatment decisions should be individualized based on the prescriber's assessment of patient risk. ***Table 3*** lists risk factors associated with more severe COVID-19 outcomes where antiviral therapy is recommended. ***Table 4*** lists risk factors where antiviral therapy may be considered. The risk of progression to severe COVID-19 depends on by the quantity of underlying medical conditions and how controlled the medical conditions are.[1,8,17–21] A greater number of risk factors are associated with a higher risk of severe COVID-19 outcomes and not all medical conditions carry the same risk.[17,19,22]

3. **Nirmatrelvir/ritonavir is the preferred first-line therapy** for treating patients with mild to moderate COVID-19 who are at high risk of severe COVID-19 due to feasibility of administration.
    - Recommend starting treatment within **5 days** of symptom onset.
    - Nirmatrelvir/ritonavir tablets can be crushed. A feeding tube is not a contraindication to use.[23]
    - For patients with renal impairment or on dialysis, dose adjustments can be made (See ***Table 5***).
    - 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 (See ***Table 5*** for suggested resources).
        - Consult with specialists as required (e.g., oncology, transplant, infectious diseases).
        - Consult with a pharmacist who can obtain a complete medication, recreational, and natural health product history from the patient is recommended.

4. **Remdesivir is an alternative when nirmatrelvir/ritonavir cannot be used** (e.g., medical contraindications, significant drug-drug interactions that cannot be mitigated, symptom onset greater than 5 days but within 7 days) for patients with mild to moderate COVID-19.
    - Recommend starting treatment within **7 days** of symptom onset.
    - Patients need to be able to receive 3 days of consecutive IV therapy. Consider travel requirements or other delivery barriers that may exist.

Table 3: Risk Factors Associated with More Severe COVID-19 Outcomes Where Antiviral Therapy is RECOMMENDED

Risk Factors	Description[1,8,17–19,21]
Age	• 65 years and older, regardless of vaccine status, with no other risk factors

Immunocompromised Status (Age 18 and older, regardless vaccine status or prior COVID-19 infections)	• Advanced untreated human immunodeficiency virus (HIV) or treated HIV with a CD4 count equal or less than 200/mm^3 or CD4 fraction equal or less than 15%
	• Bone marrow transplant or stem cell transplant
	• Solid organ transplant
	• Have active hematological malignancy or recently received treatment for hematological malignancy
	  - E.g., have received treatment with any anti-CD20 agents or B-cell depleting agents in the last 2 years
	• Chimeric antigen receptor (CAR) T-cell therapy in the last 6 months
	• Treatment for cancer (including solid tumors), limited to: systemic therapy in the last 6 months (e.g., chemotherapy, molecular therapy, immunotherapy, targeted therapies, monoclonal antibodies, excluding those receiving adjunctive hormonal therapy only) or radiation therapy in the last 3 months
	• Prednisone use equal to or greater than 20 mg/day (or corticosteroid equivalent) for 14 days or more, or other moderately or severely immunosuppressive therapies (e.g., alkylating agents)
	• Primary immunodeficiencies. For example:
	  - Hypogammaglobulinemia
	  - Combined immune deficiencies affecting T-cells
	  - Immune dysregulation (e.g., familial hemophagocytic lymphohistiocytosis)
	  - Type 1 interferon defects caused by a genetic primary immunodeficiency disorder or secondary to anti-interferon autoantibodies
	  - Diagnosed by an immunologist and requires ongoing immunoglobulin replacement therapy (IVIg or SCIg)
	  - Primary immunodeficiency with a confirmed genetic cause (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)

Table 4: Risk Factors Associated with More Severe COVID-19 Outcomes Where Antiviral Therapy MAY BE CONSIDERED

Risk for More Severe COVID-19 Outcomes	Number of Risk Factors**
Higher	3 or more
Moderate	2
Lower	0-1

** **Description of Risk Factors Where Antiviral Therapy May be Considered**[1,8,17–20]:

Vaccination Status:

- Have never received a COVID-19 vaccine

Medical Conditions:

- Active tuberculosis (treated or untreated)
- Cerebrovascular disease
- Chronic kidney disease, especially CKD stage 4 or 5 and dialysis
- Chronic lung diseases, limited to: asthma, bronchiectasis, 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 or type 2
- Disabilities and developmental delay, including Down syndrome
- Heart conditions (e.g., heart failure, coronary artery disease, cardiomyopathies)
- Mental health conditions, limited to: mood disorders (including depression), schizophrenia spectrum disorders
- Neurologic conditions that cause an inability to control respiratory secretions or communicate disease progression (e.g., cognitive disorders such as Alzheimer-type dementia)
- Obesity (body mass index above 30 kg/m^2)
- Pregnancy or recent pregnancy (42 days post-partum/end of pregnancy)

Certain medical or social vulnerabilities may confer an increased risk of disease progression because affected individuals may experience challenges in recognizing, communicating or acting on progressive COVID-19 symptoms.[8] People who are at a high risk of poor outcomes from COVID-19 based on social determinants of health should be considered priority populations for access to antivirals. Individuals at high risk include Indigenous people, Black people, other members of racialized communities; people experiencing intellectual, developmental, or cognitive disabilities; people who use substances regularly (e.g., alcohol); people who live with mental health conditions; and people who are underhoused.[8,17,24]

Overview of Antiviral Therapies

Table 5: Overview of Nirmatrelvir/Ritonavir and Remdesivir

Parameter	Nirmatrelvir/Ritonavir (Paxlovid)	Remdesivir (Veklury)
Place in Therapy	Preferred first-line therapy	Indicated where nirmatrelvir/ritonavir is contraindicated (e.g., drug-drug interaction that cannot be safely managed, medical contraindication) or when patients are beyond the nirmatrelvir/ritonavir initiation treatment window (i.e., symptom onset greater than 5 days but within 7 days).
Health Canada-Approved Indications	Treatment of mild to moderate COVID-19 in adults 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.[25]	Non-hospitalized adult 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.[26] Hospitalized adult and pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with COVID-19 pneumonia requiring supplemental oxygen.[26]
Prescribing Window	Adults with mild to moderate COVID-19: Within **5 days** of symptom onset	Adults with mild to moderate COVID-19: Within **7 days** of symptom onset
Mechanism of Action	Nirmatrelvir is a protease inhibitor that prevents viral replication.[25] Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir to increase plasma concentrations of nirmatrelvir.[25]	Adenosine analog prodrug that binds to SARS-CoV-2 RNA polymerase to inhibit viral replication.[26]
Clinically Relevant Contraindications	Hypersensitivity Severe hepatic impairment (Child-Pugh Class C)	Hypersensitivity Sinus bradycardia is a precaution but not a contraindication.[26]

Parameter	Nirmatrelvir/Ritonavir (Paxlovid)	Remdesivir (Veklury)
Usual Dosing	Nirmatrelvir 300 mg and ritonavir 100 mg orally twice daily for **5 days**	Adults with mild to moderate COVID-19 weighing 40 kg and greater: 200 mg IV single dose on **day 1**, then 100 mg IV once daily on **day 2** and **day 3**
 **Renal Impairment Dosing**††	**eGFR 30 mL/min to less than 60 mL/min:** • Nirmatrelvir 150 mg and ritonavir 100 mg twice daily for **5 days** **eGFR less than 30 mL/min**: • Nirmatrelvir 300 mg and ritonavir 100 mg on **day 1**, then nirmatrelvir 150 mg and ritonavir 100 mg once daily on **days 2 to 5** [27] **Hemodialysis or Peritoneal Dialysis** **For patients 40 kg and greater:** • Nirmatrelvir 300 mg and ritonavir 100 mg on **day 1**, then nirmatrelvir 150 mg and ritonavir 100 mg once daily on **days 2 to 5** (on dialysis days, dose after dialysis session)[27] **For patients less than 40 kg:** • Nirmatrelvir 150 mg and ritonavir 100 mg every 48 hours for 3 doses (on dialysis days, dose after dialysis)[27]	No dosage adjustment required for patients with any degree of renal impairment, including patients on dialysis. Remdesivir can be administered without regard to the timing of dialysis. [26]

Parameter	Nirmatrelvir/Ritonavir (Paxlovid)	Remdesivir (Veklury)
 **Liver Impairment Dosing**	No dosage adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B).[25] Nirmatrelvir/ritonavir is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) due to a lack of pharmacokinetic and safety data.[25]	No dosage adjustment is recommended for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B or C).[28] Remdesivir is not recommended in patients with ALT equal to or greater than 5 times the upper limit of normal.[26] Remdesivir may be restarted when the ALT falls to less than 5 times the upper limit of normal.[26]
Potential Drug Interactions‡‡	Nirmatrelvir and ritonavir are major CYP3A4 substrates.[1] Ritonavir is a strong CYP3A4 inhibitor.[1] Assess for drug-drug interactions and mitigation strategies (e.g., dose reductions, short-term treatment interruption). Consult with specialists (e.g., oncology, transplant, infectious diseases) as required. The Committee recommends consultation with a pharmacist who can obtain a complete medication, recreational, and natural health product history.	Minor substrate of CYP3A4 and OATP1B1 and P-glycoprotein.[1] Few clinically significant drug interactions. • Concomitant use with hydroxychloroquine or chloroquine is not recommended as they may reduce remdesivir's antiviral activity.[1] The use of beta-blockers is not a contraindication to using remdesivir.[26]
Administration Considerations	Available as a film-coated tablet that can be crushed and administered through feeding tubes if necessary.[29]	Available as an IV formulation which requires nursing support to administer on three consecutive days. Consider travel requirements or other delivery barriers that may exist.

†† Dosing recommendations may differ from Health Canada-approved dosing.

‡‡ Drug-Drug Interaction Resources:

- University of Liverpool COVID-19 Drug Interactions Checker
- University of Waterloo and University of Toronto: Nirmatrelvir/Ritonavir (Paxlovid) – What Prescribers and Pharmacists Need to Know
- University of Waterloo and University of Toronto: Paxlovid for a Patient on a Direct Oral Anticoagulant
- University Health Network/Kingston Health Sciences Centre: Nirmatrelvir/Ritonavir (Paxlovid) Drug-Drug Interactions in Oncology

For information on the use for nirmatrelvir/ritonavir and remdesivir in patients with COVID-19 who are pregnant or breastfeeding/chestfeeding, refer to the Frequently Asked Questions on Antiviral Therapy for Adults with Mild to Moderate COVID-19.

Evidence Summary

Evidence Summary for Nirmatrelvir/Ritonavir

The EPIC-HR randomized controlled trial showed nirmatrelvir/ritonavir treatment in non-hospitalized adults with mild to moderate COVID-19 who were started on treatment within 5 days of symptom onset reduced the risk of COVID-19-related hospitalization or death compared to placebo.[12] The generalizability of the EPIC-HR trial results to current clinical practice is limited because the patients enrolled were unvaccinated, infected by COVID-19 variants different from those currently circulating and the trial excluded patients who developed natural immunity from previous COVID-19 infection.[30]

Since the emergence of Omicron and its sub-variants, prospective, observational and retrospective real-world studies reported nirmatrelvir/ritonavir treatment was associated with decreased hospitalization and mortality in high-risk patients, including immunocompromised patients and patients with varying vaccination status compared with no treatment or standard of care.[14,31] Observational studies have also found treatment with nirmatrelvir/ritonavir was associated with a reduced risk of emergency department visits compared to no treatment or standard of care.[14]

Age has historically been one of the strongest risk factors for severe COVID-19 outcomes.[17] However, a population-based cohort study from British Columbia (B.C.) found nirmatrelvir/ritonavir treatment was not associated with decreased mortality and hospitalization in individuals who were not moderately or severely immunocompromised, including those aged 70 years or older with a serious medical condition that increased their risk for progression to severe COVID-19.[30] The greatest benefit was observed in moderately or severely immunocompromised individuals, irrespective of age.[30] Two population-based cohort studies from Ontario and Quebec found nirmatrelvir/ritonavir treatment was associated with decreased hospitalization and mortality in patients 70 years and older with COVID-19 compared to no nirmatrelvir/ritonavir treatment.[32,33] However, these studies were limited by the lack of a subgroup analysis that stratified patients by both age and comorbidities to determine whether the beneficial association with nirmatrelvir/ritonavir would have persisted in individuals 70 years and older after accounting for other comorbidities.

Results from observational studies suggest nirmatrelvir/ritonavir was comparable to remdesivir in reducing the risk of hospitalization for COVID-19 or death in non-hospitalized patients with COVID-19.[14]

For additional information on selected studies on nirmatrelvir/ritonavir, refer to ***Appendix A*****.**

Evidence Summary for Remdesivir

The PINETREE randomized control trial showed remdesivir reduced the risk of COVID-19-related hospitalization or COVID-19-related medical visits compared to placebo in unvaccinated, non-hospitalized adults with mild to moderate COVID-19 who were started on treatment within 7 days of symptom onset.[11] The generalizability of the results from the PINETREE trial to current clinical practice is limited because the trial excluded vaccinated patients.

Although PINETREE was conducted before the emergence of the Delta and Omicron variants, observational studies during the Omicron era found remdesivir to be associated with decreased hospitalization and emergency department visits compared to no remdesivir treatment.[13] An observational study also suggested remdesivir may decrease the need for supplemental oxygen and was associated with a reduced prevalence of COVID-19 sequelae compared to no remdesivir treatment.[13,34] The extent of clinical benefit of remdesivir in individuals with prior immunity remains unknown, as the risk of progression to severe COVID-19 is reduced by immune protection.[9] Multivariate analyses were not conducted in the observational studies to determine whether the beneficial association with remdesivir was consistent across strata of age or after adjusting for selected comorbidities (e.g., immunocompromised status).

Remdesivir appears to be clinically comparable to nirmatrelvir/ritonavir for predominantly vaccinated, high-risk, non-hospitalized patients with COVID-19 during the Omicron era.[13,24,34–36]

For additional information on selected studies on remdesivir, refer to ***Appendix B***.

Additional Resources

- Frequently Asked Questions on Antiviral Therapy for Adults with Mild to Moderate COVID-19
- Visit the Ontario Health COVID-19 treatment website for the latest resources about nirmatrelvir/ritonavir, remdesivir and other COVID-19 therapeutics, including information on how to access to COVID-19 therapeutics for patients in the community.
- Nirmatrelvir/ritonavir product monograph
- Remdesivir product monograph
- Ministry of Health: COVID-19 Guidance for Public Health Units: Long-Term Care Homes, Retirement Homes, and Other Congregate Living Settings
- Public Health Ontario: Outbreak Preparedness, Prevention and Management in Congregate Living Settings
- National Advisory Committee: COVID-19 immunization guidance

Questions

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

Appendices

Appendix A. Highlights of Selected Studies on Nirmatrelvir/Ritonavir

EPIC-HR was a multi-centre, randomized, double-blind, placebo-controlled trial in 2,246 unvaccinated, non-hospitalized adults with confirmed SARS-CoV-2 within five days of symptom onset and at least one risk factor for progression to severe COVID-19.[12] Patients were randomized to receive a 5-day course of oral nirmatrelvir 300 mg in combination with ritonavir 100 mg or placebo. Nirmatrelvir/ritonavir decreased the risk of COVID-19-related hospitalization or death from any cause through day 28 compared to placebo (87.8% relative risk reduction [0.78% vs 6.4%], 95% CI −7.21 to −4.03, p<0.001). The number needed to treat (NNT) to prevent one case of hospitalization or death was 18 with nirmatrelvir/ritonavir compared to placebo.[12] Nirmatrelvir/ritonavir was generally well-tolerated. Mild to moderate dysgeusia (distorted sense of taste), diarrhea, increased fibrin D-dimer and increased alanine aminotransferase were the most common adverse effects. Few of the reported adverse effects led to discontinuation of the study drug.[12]

During the Omicron era when BA.2, BA.5 and BQ1 were the dominant circulating subvariants, a population-based cohort study of 6,866 non-hospitalized adults with mild to moderate COVID-19 was conducted in B.C.[30,37] Over 90% of individuals were vaccinated against COVID-19. Nirmatrelvir/ritonavir treatment was associated with a statistically significant decreased risk of death from any cause or COVID-19-related hospitalization through day 28 compared to no nirmatrelvir/ritonavir treatment in moderately immunocompromised individuals (risk difference [RD] −2.5%, 95% CI −4.8% to −0.2%) and severely immunocompromised individuals (RD −1.7%, 95% CI −2.9% to −0.5%).[30] However, the risk reduction was not statistically significant in non-immunocompromised individuals with medical conditions associated with a high risk for complications from COVID-19.[30] The risk reduction was also not observed in selected high-risk individuals (e.g., unvaccinated patients older than 70 years old, or fully vaccinated patients older than 70 years who had a serious medical condition that increased their risk for progression to severe COVID-19).[30] In a subgroup analysis of individuals 70 years and older, nirmatrelvir/ritonavir was not associated with a decreased risk of death from any cause or COVID-19-related hospitalization after accounting for other comorbidities compared to no nirmatrelvir/ritonavir treatment.[30]

A population-based cohort study was also conducted in Ontario of 177,545 non-hospitalized adults with mild to moderate COVID-19 during the Omicron era when the prevalent circulating subvariants were BA.2, BA.4 and BA.5.[32] Nirmatrelvir/ritonavir treatment was associated with a statistically significant lower risk of death from any cause or hospital admission from COVID-19 through day 30 compared to no nirmatrelvir/ritonavir treatment (2.1% vs 3.7%; weighted OR 0.56, 95% CI 0.47 to 0.67).[32] The findings were consistent across strata of age (e.g., less than 70 years old compared to 70 years and older), vaccination status and comorbidities.[32] However, the study did not conduct a subgroup analysis combining strata of age and immunocompromised status to

examine the magnitude of effect from nirmatrelvir/ritonavir treatment in patients with different combinations of the two specific risk factors (e.g., immunocompromised patients age 70 years and older compared to non-immunocompromised patients age 70 years and older). The unknown number of patients in the untreated group who might have received remdesivir was a limitation of this study.[32]

In Quebec, a population-based cohort study of 16,804 non-hospitalized adults with mild to moderate COVID-19 was conducted during the Omicron era when BA.2, BA.4 and BA.5 were the dominant circulating subvariants to determine the real-world effectiveness of nirmatrelvir/ritonavir on COVID-19-associated hospitalization through day 30.[33] Nirmatrelvir/ritonavir treatment was associated with a 69% relative risk reduction (RR) for hospitalization compared to no nirmatrelvir/ritonavir treatment (RR 0.31, 95% CI 0.28 to 0.36; NNT=13).[33] In severely immunocompromised patients, nirmatrelvir/ritonavir treatment was associated with a significantly decreased risk of hospitalization compared to no nirmatrelvir/ritonavir treatment (RR 0.66, 95% CI 0.50 to 0.89; NNT=16).[33] For patients aged 70 years and older, nirmatrelvir/ritonavir treatment was associated with a 25% relative RR for hospitalization compared to no nirmatrelvir/ritonavir treatment (RR 0.75, 95% CI 0.63 to 0.88; p=0.001; NNT=28, 95% CI 18 to 68).[33] However, the study did not conduct a subgroup analysis combining the strata of age and immunocompromised status to examine the magnitude of effect from nirmatrelvir/ritonavir treatment in patients with different combinations of the two specific risk factors (e.g., immunocompromised patients age 70 years and older compared to non-immunocompromised patients age 70 years and older). Nirmatrelvir/ritonavir treatment was associated with a significantly decreased risk of hospitalization compared to no nirmatrelvir/ritonavir treatment in patients with incomplete primary vaccination (RR 0.04, 95% CI 0.03 to 0.06; NNT=8).[33] At the time, primary vaccination was defined as two or more vaccine doses and it was prior to the availability of the BA.4/BA.5 bivalent and XBB.1.5 vaccines.[33] For individuals with complete primary vaccination, no beneficial association for nirmatrelvir/ritonavir treatment was observed compared to no nirmatrelvir/ritonavir treatment.[33]

The EPIC-SR study was a randomized controlled trial to assess the effectiveness of nirmatrelvir/ritonavir compared with placebo in adults with mild to moderate COVID-19 at standard risk for developing severe COVID-19.[15] It included 1,296 patients who were either vaccinated against COVID-19 but with an increased risk of developing severe illness, or unvaccinated with no risk factors for progression to severe disease.[15] There was no significant difference found between the two treatment groups for the primary outcome of self-reported, sustained alleviation of all COVID-19 signs and symptoms through day 28.[15] The incidences of COVID-19-related medical visits, hospitalization and death through day 28 were very low for both treatment groups.[15]

Appendix B. Highlights of Selected Studies on Remdesivir

Evidence to support IV remdesivir treatment in patients with mild to moderate COVID-19 is primarily based on the PINETREE trial. PINETREE was a randomized, double-blind, placebo-controlled trial in 562 unvaccinated, non-hospitalized patients who were positive for COVID-19, had symptom onset within the previous seven days, and were considered at high risk because they had at least one risk factor for disease progression.[11] Patients were randomized to receive a 3-day course of IV remdesivir or placebo. The risk of COVID-19-related hospitalization or death from any cause by day 28 was 87% lower in the remdesivir group compared to the placebo group (HR 0.13, 95% CI 0.03 to 0.59; p=0.008).[11] The data were driven by a decreased risk of hospitalization because there were no deaths in either treatment group.[11] The composite secondary endpoint of a COVID-19-related medical visit or death through day 28 was lower in the remdesivir group compared to the placebo group (HR 0.19, 95% CI 0.07 to 0.56; p=0.008).[11] This outcome was driven by a decreased risk of COVID-19-related medical visits as there were no deaths in either treatment group.[11] There was no significant difference between the two treatment groups for mean viral load decrease at day seven.[11] Remdesivir was well-tolerated. Mild nausea, headache and cough were the most common side effects [11,13] Serious adverse events leading to drug discontinuation were uncommon in the PINETREE trial and other observational studies of remdesivir.[11,13]

A retrospective cohort study of 681 non-hospitalized adults with mild to moderate COVID-19 was conducted during the Omicron era to determine the real-world effectiveness of remdesivir treatment compared to no remdesivir.[34] 65.1% of the patients were vaccinated against COVID-19 and 6.2% of the patients had a previous COVID-19 infection.[34] Patients treated with remdesivir were associated with a significantly reduced risk of hospitalization (adjusted OR=0.049, 95% CI 0.015 to 0.163; p<0.001), disease progression leading to oxygen requirement (adjusted OR=0.034, 95% CI 0.008 to 0.144; p<0.001) and duration of COVID-19 symptoms (adjusted β=–5.106, 95% CI –5.821 to –4.391; p<0.001) during the acute infection compared to no remdesivir treatment.[34]

Another small, retrospective cohort study of 170 non-hospitalized adults with mild to moderate COVID-19 was conducted when the Omicron B.1.1.529 subvariant was the predominant circulating strain.[35] 64% of the patients were vaccinated against COVID-19.[35] Compared to no remdesivir treatment, remdesivir treatment was associated with a significantly reduced risk of COVID-19-related hospitalization and/or emergency department visits through day 29 (OR=0.41, 95% CI 0.17–0.95; p=0.04).[35] The benefit of remdesivir was driven by the reduction in emergency department visits.[35]

A prospective, observational study was conducted in Ontario of 192 non-hospitalized adults with solid organ transplant and mild to moderate COVID-19 when the Omicron BA.2 subvariant was the predominant circulating strain. 90.1% of the patients had received three or more COVID-19 vaccine doses.[36] Compared to supportive care without remdesivir therapy, remdesivir treatment was associated with a significantly reduced risk of COVID-19-related hospitalization for greater than 24 hours within 30 days of symptom onset (HR=0.12, 95% CI 0.03 to 0.47; p=0.013).[36] The greatest benefit was observed in the subgroup of lung transplant patients.[36] The NNT to treat to prevent one hospital admission was 15.2 (95% CI 13.6-31.4).[36] None of the patients in the study died or required ICU care.[36] Due to the low event rate for hospitalization, the authors did not

perform a multivariable analysis to adjust for the effect of each variable (e.g., age, lung transplant, diabetes, coronary artery disease, chronic kidney disease, number of comorbidities, treatment with prednisone or treatment with remdesivir).[36]

References

1. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Internet]. 2023 [cited 2023 Nov 13].
2. Agarwal A, Hunt BJ, Stegemann M, Rochwerg B, Lamontagne F, Siemieniuk RA, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020 Sep 4;m3379.
3. BC Centre for Disease Control. Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19 [Internet]. 2023 [cited 2023 Nov 20]. Available from: bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/ClinicalPracticeGuide_Therapeutics_MildModerateCOVID.pdf
4. Alberta Health Services. Therapeutic Management of Adult Patients with COVID-19 [Internet]. 2022 [cited 2023 Nov 6]. Available from: albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-therapeutic-management-summary.pdf
5. University of Sasketchewan medSask. COVID-19 Treatments [Internet]. 2022 [cited 2023 Dec 7]. Available from: medsask.usask.ca/professional-practice/paxlovid-hcp/prescribing-paxlovid-for-covid-19.php
6. Shared Health Manitoba. Recommendations for COVID-19 Treatment - Update October 2023 [Internet]. 2023 [cited 2023 Dec 6]. Available from: sharedhealthmb.ca/files/covid-19-treatment-recommendations.pdf
7. Nova Scotia Health. NS Health COVID-19 Medication Recommendations [Internet]. 2023 [cited 2023 Dec 7]. Available from: policy.nshealth.ca/Site_Published/covid19/document_render.aspx?documentRender.IdType=6&documentRender.GenericField=&documentRender.Id=85287
8. Public Health Agency of Canada. COVID-19 signs, symptoms and severity of disease: A clinician guide [Internet]. 2022 [cited 2023 Nov 17]. Available from: canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/signs-symptoms-severity.html#a1
9. Meyerowitz EA, Scott J, Richterman A, Male V, Cevik M. Clinical course and management of COVID-19 in the era of widespread population immunity. Nat Rev Microbiol [Internet]. 2023 Dec 19 [cited 2023 Dec 24]; Available from: nature.com/articles/s41579-023-01001-1
10. Toussi SS, Hammond JL, Gerstenberger BS, Anderson AS. Therapeutics for COVID-19. Nat Microbiol. 2023 May 4;8(5):771–86.
11. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2022 Jan 27;386(4):305–15.
12. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Apr 14;386(15):1397–408.

13. Wang X, Kelly S, Peterson J, Bai Z, Loshak H, Brouwers M, et al. Remdesivir for the Treatment of COVID-19 in the Outpatient Setting [Internet]. Canadian Agency for Drugs and Technologies in Health; 2023. Available from: cadth.ca/sites/default/files/covid-19/Bundle%20covid%2019/remdesivir_for_the_treatment_of_COVID-19_in_the_outpatient_setting_systematic%20_review.pdf

14. Eze N, Asante B, Spry C, Clement F. Nirmatrelvir-Ritonavir for the Treatment of COVID-19 [Internet]. Canadian Agency for Drugs and Technologies in Health; 2023 [cited 2023 Nov 20]. Available from: cadth.ca/sites/default/files/covid-19/Bundle%20covid%2019/nirmatrelvir_ritonavir_for_treatment_of_covid-19_systematic%20review.pdf

15. Hammond J, Fountaine RJ, Yunis C, Fleishaker D, Almas M, Bao W, et al. Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19. N Engl J Med. 2024 Apr 4;390(13):1186–95.

16. Agarwal A, Hunt BJ, Stegemann M, Rochwerg B, Lamontagne F, Siemieniuk RA, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020 Sep 4;m3379.

17. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals [Internet]. 2023 [cited 2023 Nov 15]. Available from: cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

18. Public Health Agency of Canada. People who are at risk of more severe disease or outcomes from COVID-19 [Internet]. 2023 [cited 2023 Nov 17]. Available from: canada.ca/en/public-health/services/publications/diseases-conditions/people-high-risk-for-severe-illness-covid-19.html

19. U.S. Department of Health and Human Services. Federal Response to COVID-19: Therapeutics Clinical Implementation Guide [Internet]. 2023 [cited 2024 Jan 30]. Available from: aspr.hhs.gov/COVID-19/Therapeutics/Documents/USG-COVID19-Tx-Playbook.pdf

20. BC COVID Therapeutics Committee. Practice Tool #1 - Assesssment Guide for Clinicians [Internet]. 2023 [cited 2024 Jan 30]. Available from: bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/PracticeTool1_AssessmentGuideforClinicians.pdf

21. BC COVID Therapeutics Committee. Practice Tool #2 - Definitions of CEV/Immunosuppressed [Internet]. 2024 [cited 2024 Jan 30]. Available from: bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/PracticeTool2_CEVCriteria.pdf

22. Agrawal U, Bedston S, McCowan C, Oke J, Patterson L, Robertson C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. Lancet. 2022 Oct 15;400(10360):1305–20.

23. BC COVID Therapeutics Committee (CTC) COVID Therapy Review and Advisory Working Group (CTRAWG). Therapeutic Brief: Crushing Nirmatrelvir/ritonavir (Paxlovid) [Internet]. 2022 [cited 2023 Dec 5]. Available from: bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/Crushing_Paxlovid.pdf

24. Ontario Health. Ontario Health Recommendations for Outpatient Use of Intravenous Remdesivir (Veklury) in Adults [Internet]. Ontario Health; 2023 [cited 2023 Nov 14]. Available from: ontariohealth.ca/sites/ontariohealth/files/Ontario%20Health%20Recommendations%20-%20Outpatient%20Use%20of%20Intravenous%20Remdesivir%20%28Veklury%29%20in%20Adults.pdf

25. Pfizer Canada ULC. Paxlovid Product Monograph [Internet]. 2023 [cited 2023 Nov 20]. Available from: pdf.hres.ca/dpd_pm/00072671.PDF

26. Gilead Sciences Canada. Veklury Product Monograph [Internet]. 2023 [cited 2023 Nov 20]. Available from: pdf.hres.ca/dpd_pm/00073413.PDF

27. Ontario Health (Ontario Renal Network). COVID-19 Supplemental Clinical Guidance #4: Nirmatrelvir/Ritonavir (Paxlovid) Use in Patients With Advanced Chronic Kidney Disease and Patients on Dialysis with COVID-19 [Internet]. 2022 [cited 2023 Nov 20]. Available from: ontariohealth.ca/sites/ontariohealth/files/2022-04/PaxlovidClinicalGuide.pdf

28. Gilead Sciences. Veklury (remdesivir) for injection, for intravenous use [Internet]. 2023 [cited 2023 Nov 20]. Available from: gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf

29. British Columbia COVID-19 Therapeutics Committee, COVID-19 Therapeutics Review and Advisory Working Group. Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19 [Internet]. 2023 [cited 2023 Nov 14]. Available from: bccdc.ca/Health-Professionals-Site/Documents/Antimicrobial-Immunomodulatory-Therapy-adults.pdf

30. Dormuth CR, Kim JD, Fisher A, Piszczek J, Kuo IF. Nirmatrelvir-Ritonavir and COVID-19 Mortality and Hospitalization Among Patients With Vulnerability to COVID-19 Complications. JAMA Netw Open. 2023 Oct 2;6(10):e2336678.

31. Shah MM, Joyce B, Plumb ID, Sahakian S, Feldstein LR, Barkley E, et al. Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 — United States, April–September 2022. MMWR Morb Mortal Wkly Rep. 2022 Dec 2;71(48):1531–7.

32. Schwartz KL, Wang J, Tadrous M, Langford BJ, Daneman N, Leung V, et al. Population-based evaluation of the effectiveness of nirmatrelvir–ritonavir for reducing hospital admissions and mortality from COVID-19. CMAJ. 2023 Feb 13;195(6):E220–6.

33. Kaboré JL, Laffont B, Diop M, Tardif MR, Turgeon AF, Dumaresq J, et al. Real-World Effectiveness of Nirmatrelvir/Ritonavir on Coronavirus Disease 2019-Associated Hospitalization Prevention: A Population-based Cohort Study in the Province of Quebec, Canada. Clin Infect Dis. 2023 Sep 18;77(6):805–15.

34. Mazzitelli M, Trunfio M, Sasset L, Scaglione V, Ferrari A, Mengato D, et al. Risk of hospitalization and sequelae in patients with COVID-19 treated with 3-day early remdesivir vs. controls in the vaccine and Omicron era: A real-life cohort study. J Med Virol. 2023 Mar;95(3):e28660.

35. Piccicacco N, Zeitler K, Ing A, Montero J, Faughn J, Silbert S, et al. Real-world effectiveness of early remdesivir and sotrovimab in the highest-risk COVID-19 outpatients during the Omicron surge. J Antimicrob Chemother. 2022 Sep 30;77(10):2693–700.

36. Solera JT, Árbol BG, Bahinskaya I, Marks N, Humar A, Kumar D. Short-course early outpatient remdesivir prevents severe disease due to COVID-19 in organ transplant recipients during the omicron BA.2 wave. Am J Transplant. 2023 Jan;23(1):78–83.

37. BC Centre for Disease Control. Weekly Update on Variants of Concern [Internet]. 2023 [cited 2023 Dec 27]. Available from: bccdc.ca/Health-Info-Site/Documents/VoC/VoC_Weekly_report_20230222.pdf