CADTH Reimbursement Recommendation

Nirmatrelvir-Ritonavir (Paxlovid)

**Indication:** For the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death

**Sponsor:** Pfizer Canada ULC

**Final recommendation:** Reimburse with conditions
What Is the CADTH Reimbursement Recommendation for Paxlovid?
CADTH recommends that Paxlovid be reimbursed by public drug plans for the treatment of mild to moderate COVID-19 in adults with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death, if certain conditions are met.

Which Patients Are Eligible for Coverage?
Paxlovid should only be covered to treat patients who have severe or moderate immunosuppression as described in Table 1. Treatment should be initiated as soon as possible within 5 days of symptom onset.

What Are the Conditions for Reimbursement?
Paxlovid should only be reimbursed if the cost is reduced.

Why Did CADTH Make This Recommendation?
• Evidence from 2 observational studies suggested that patients with moderate to severe immune suppression who have COVID-19 could benefit from Paxlovid for preventing hospitalization and death. There is uncertainty about whether these findings reflect the actual benefits of Paxlovid because observational studies may be influenced by external confounding factors that may impact the results.
• Paxlovid meets patients’ unmet needs by reducing the risk of hospitalization or death in those who have moderate to severe immune suppression and are, therefore, at risk of complications from progressing to severe COVID-19.
• Based on CADTH’s assessment of the health economic evidence, Paxlovid does not represent good value to the health care system at the public list price. A price reduction is therefore required.
• Based on public list prices, Paxlovid is estimated to cost the public drug plans more than $40 million per year over the next 3 years.

Additional Information
What Is COVID-19?
COVID-19 is an illness caused by SARS-CoV-2, the rapid global spread of which led to a pandemic in March 2020. Although the majority of people who have COVID-19 experience mild symptoms, COVID-19 can lead to serious medical complications associated with high morbidity and mortality. The risk factors affecting the progression to severe disease have
Summary

evolved over time. Population immunity has been building, and the number and characteristics of patients hospitalized due to COVID-19 has changed. According to the recently updated WHO living guideline, patients at high risk of serious complications have a compromised immune system, with a current 6% hospitalization rate.

Unmet Needs in COVID-19
Several patient groups expressed a need for treatments that are effective at reducing the risk of hospitalization and death caused by the variants of COVID-19 currently circulating. Patients at high risk for progression to severe COVID-19, many of whom live with existing acute or chronic conditions, expressed the need for a treatment that does not have contraindications with their current treatments.

How Much Does Paxlovid Cost?
Treatment with Paxlovid is expected to cost more than $100 million per year over the next 3 years but could be as high as $200 million per year as reported by the sponsor.
Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that nirmatrelvir-ritonavir be reimbursed for the treatment of mild to moderate COVID-19 in adults with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

CDEC recognized that in patients who are at high risk for progression to severe COVID-19 there is a need for an intervention that reduces hospitalization and death.

CDEC also recognized that nirmatrelvir-ritonavir is currently available across all jurisdictions and considered the prevailing and contemporary nature of the disease that has evolved over time. Several sources of evidence were considered by the committee to better reflect the current state of COVID-19. Observational studies by Schwartz et al., which enrolled patients from Ontario, and Dormuth et al., which enrolled patients from British Columbia, are more contemporaneous, require interpreting subgroup effects to isolate populations where benefit may be plausible, although these data must be interpreted with caution, due to the reliability of interpreting subgroup effects in observational studies and the possibility of residual confounding. Results from these studies suggest that patients with moderate to severe immune suppression who have received prior vaccination could potentially benefit from nirmatrelvir-ritonavir for preventing hospitalization and death. Overall, the observational data showed that the effectiveness of nirmatrelvir-ritonavir is considerably reduced in the general population who are adequately vaccinated, in younger patients, and in patients who are not immunocompromised. In the Dormuth et al. study, treatment with nirmatrelvir-ritonavir was associated with statistically significant relative reductions in prevention of death or admission to hospital in patients who were severely immunocompromised compared to patients who did not receive nirmatrelvir-ritonavir (risk difference [RD] = −2.5%; 95% confidence interval [CI], −4.8% to −0.2%) and in patients who were moderately immunocompromised (RD = −1.7%; 95% CI, −2.9% to −0.5%). Two other patient groups were assessed in the Dormuth et al. study: a group of patients who were not immunocompromised but had medical conditions associated with a high risk for complications from COVID-19 and a group of patients who were at lower risk of COVID-19–related complications than the other groups but had risk factors that put them at higher risk of complications than the general population (e.g., those older than 70 years who were unvaccinated). In both patient groups, there were no statistically significant differences between those patients exposed to nirmatrelvir-ritonavir versus those who were not.

Several patient groups expressed a need for treatments that are effective against the newer variants of COVID-19. Because patients who are at high risk for progression to severe COVID-19 often live with an existing acute or chronic condition(s), these patients expressed a need for a treatment that does not present contraindications with their current medications and therapies. CDEC noted that nirmatrelvir-ritonavir could potentially address some of these needs in patients with moderate to severe immune suppression.
The committee considered the analysis conducted by CADTH in which the cost-effectiveness of nirmatrelvir-ritonavir plus standard of care relative to standard of care alone was based on observational data from the Schwartz et al. study; the Dormuth et al. study was not yet published at the time of the submission. Based on the sponsor’s submitted price for nirmatrelvir-ritonavir and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) was $442,082 per quality-adjusted life-year (QALY) gained compared with standard of care alone. A price reduction would be required for nirmatrelvir-ritonavir to achieve an ICER of $50,000 per QALY. There is uncertainty in the estimation of the price reduction due to the limitations in the clinical evidence base.

Table 1: Reimbursement Conditions and Reasons

<table>
<thead>
<tr>
<th>Reimbursement condition</th>
<th>Reason</th>
<th>Implementation guidance</th>
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<tbody>
<tr>
<td><strong>Initiation</strong></td>
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<tr>
<td>1. Treatment with nirmatrelvir-ritonavir should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset in adult patients who have either of the following:</td>
<td>Definition for severely immunosuppressed and moderately immunosuppressed was used by Dormuth et al. who found a statistically significant benefit the primary composite end point of death from any cause and COVID-19–related hospitalization.(^9)</td>
<td>CDEC noted that the Health Canada indication states that nirmatrelvir-ritonavir should be initiated as soon as possible after a diagnosis of COVID-19 based on a positive test (either using RAT or PCR) has been made, and within 5 days of symptom onset, which may be an implementation challenge in jurisdictions where no routine outpatient testing is no longer provided. CDEC recognizes that the list of examples in sections 1.1 and 1.2 of the reimbursement conditions for moderate or severe immunosuppression is not comprehensive. Patients who are moderately or severely immunocompromised but whose condition is not listed in sections 1.1 and 1.2 may also be eligible for treatment with nirmatrelvir-ritonavir.</td>
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<tr>
<td>1.1. Severe immunosuppression, such as:</td>
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<td>• recipient of solid organ transplant(^a)</td>
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<td>• treatment for a malignant hematologic condition(^b)</td>
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<td>• bone marrow–, stem cell transplant–, or transplant-related immunosuppressant use(^c)</td>
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<td>• receipt of anti-CD20 drugs or B cell–depleting drugs (such as rituximab) in the past 2 years.</td>
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<td>• severe primary immunodeficiencies(^d)</td>
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<td>1.2. Moderate immunosuppression, such as:</td>
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<td>• treatment for cancer, including solid tumours</td>
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<td>• treatment with significantly immuno-suppressing drugs (e.g., a biologic in the past 3 months, oral immune-suppressing medication in the past months, oral steroid [20 mg/day of prednisone equivalent taken on an ongoing basis] in the past month, or immune-suppressing infusion or injection in the past 3 months).</td>
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<td>• advanced HIV infection (treated or untreated)(^e)</td>
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### CADTH Reimbursement Recommendation

<table>
<thead>
<tr>
<th>Reimbursement condition</th>
<th>Reason</th>
<th>Implementation guidance</th>
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| • moderate primary immunodeficiencies<sup>f</sup>  
• renal conditions (i.e., hemodialysis, peritoneal dialysis, glomerulonephritis and dispensing of a steroid, eGFR < 15 mL/min/1.73 m<sup>2</sup>) |        |                          |

#### Pricing

2. A reduction in price.

The ICER for nirmatrelvir-ritonavir was estimated to be $442,082 per QALY gained when compared with standard of care alone. A price reduction of at least 62% would be required for nirmatrelvir-ritonavir to achieve an ICER of $50,000 per QALY gained. There is uncertainty in the estimation of the price reduction due to the limitations in the clinical evidence base.

#### Feasibility of adoption

3. The feasibility of adoption of nirmatrelvir-ritonavir must be addressed.

At the submitted price, the incremental budget impact of nirmatrelvir-ritonavir is expected to be greater than $40 million in each of years 1, 2, and 3 of the analysis.

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CDEC = Canadian Drug Expert Committee; eGFR = estimated glomerular filtration rate; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; RAT = rapid antigen test.

<sup>a</sup>Presence of a diagnosis, procedure, or fee code for solid organ transplant of kidney, liver, lung, heart, pancreas or islet cell, bowel, or any combination at any time.

<sup>b</sup>Presence of a diagnosis code for a hematologic condition and a procedure or fee code for chemotherapy or immunotherapy in the past year or presence of a primary diagnosis code for a hematologic condition in a hospital episode in the past year.

<sup>c</sup>Presence of a diagnosis, procedure, or fee code for bone marrow transplant or stem cell transplant in the past 2 years, or dispensing or remaining days supply of an immunosuppressant in the past 3 months and presence of a diagnosis, procedure, or fee code for bone marrow transplant or stem cell transplant in the past 5 years.

<sup>d</sup>Severe immunodeficiencies include combined immunodeficiencies affecting T cells, immune dysregulation (particularly familial hemophagocytic lymphohistiocytosis), or type 1 interferon defects (caused by a genetic primary immunodeficiency disorder or secondary to anti-interferon autoantibodies).

<sup>e</sup>Presence of a diagnosis code (2 Medical Services Plan [MSP]) or 1 Discharge Abstract Database [DAD] and National Ambulatory Care Reporting System [NACRS]) for AIDS at any time or presence of 1 MSP diagnosis for AIDS within 2 weeks after a CD4 lab test or presence of a CD4 lab test result with CD4 count ≤ 200/mm<sup>3</sup> or CD4 fraction ≤ 15% at any time.

<sup>f</sup>Presence of diagnosis code for a primary immunodeficiency with a genetic cause at any time or presence of diagnosis code for a primary immunodeficiency and presence of a procedure code for immunoglobulin replacement therapy in the past year.


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**Discussion Points**

- The sponsor requested a reconsideration of the initial CDEC draft recommendation to reimburse with conditions nirmatrelvir-ritonavir for the 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. CDEC discussed each of the issues identified by the sponsor in their request for reconsideration.
During the initial and reconsideration meetings, CDEC recognized that patients who are at increased risk for severe COVID-19 need access to treatments that are effective against COVID-19. Because individuals who have a higher risk for severe COVID-19 often live with an existing acute or chronic condition(s), these individuals need a variety of treatments that do not present contraindications with their current therapies. In addition, patients need treatments that are effective against different variants of COVID-19.

CDEC noted that there is a difference between high or higher risk of hospitalization and death, and those who would actually benefit from nirmatrelvir-ritonavir. In its deliberations, CDEC considered the evidence available and its relevance to the real-world disease context.

During the initial and reconsideration meetings, CDEC acknowledged national and international guidelines that indicate older adults (age thresholds varying from 60 years to 80 years), individuals with underlying medical conditions, and residents of long-term care facilities and other congregate living settings are at an elevated risk for severe outcomes, such as hospitalization and death. This CDEC recommendation is based on the available evidence and its relevance to the real-world disease context, which suggests that patients with moderate to severe immune suppression could potentially benefit from nirmatrelvir-ritonavir for preventing hospitalization and death. However, CDEC also noted that the available evidence does not indicate that older adults, based on age alone or living in long-term care facilities, would benefit from nirmatrelvir-ritonavir.

During the initial and reconsideration meetings, CDEC discussed that there is a lack of evidence on the safety of nirmatrelvir-ritonavir, especially in patients who are older and/or frail who may also be taking other medications and are therefore at higher risk for significant drug interactions.

During the initial and reconsideration meetings, risk factors involved in the progression to severe COVID-19 have changed over time. Earlier in the pandemic, a wide range of risk factors were identified, which included older age, cardiovascular disease, diabetes mellitus, hypertension, cerebrovascular disease, dementia, neurodevelopmental disorders, and chronic kidney disease. CDEC also noted that at the time of issuing this recommendation, the relevance of these risk factors for progressing to severe disease has changed; as population immunity has increased over time and with the emergence of new variants, the proportion and characteristics of patients being hospitalized or dying due to COVID-19 have evolved.

During the initial and reconsideration meetings, CDEC discussed that results from the pivotal phase III trial (EPIC-HR) were not informative in determining the efficacy of nirmatrelvir-ritonavir in contemporary COVID-19 infection in Canada due to external validity limitations in the study. These were the population enrolled in EPIC-HR does not represent the population at risk for severe COVID-19 infection in 2024 due to changes in factors considered to put a patient at high risk of severe COVID-19 infection, there are now different circulating strains with differing virulence (delta versus omicron), and patients with prior infection or vaccination were excluded.

During the reconsideration meeting, CDEC recognized that new evidence and data for the treatment of COVID-19 are regularly published. CDEC noted that this recommendation is based on the evidence...
available during the CDEC discussion held in December 2023. CDEC expects the role of nirmatrelvir-ritonavir in different patient populations will be further clarified as new evidence emerges.

- Recognizing that previous advice and guidance on the use of nirmatrelvir-ritonavir are available (such as the CADTH Drug Implementation Advice for Nirmatrelvir-Ritonavir) and different reimbursement criteria for nirmatrelvir-ritonavir currently implemented, CDEC discussed that this recommendation presents a change in clinical practice and access to nirmatrelvir-ritonavir, which is due to the changing nature of the pandemic and viral evolution.

- Patients with post–COVID-19 condition (patients infected with the virus that causes COVID-19 who experience long-term effects from their infection beyond the acute infection) expressed a need for a therapy that can cure their condition and could fully eliminate COVID-19 symptoms or, at minimum, lessen the severity of symptoms and improve their health-related quality of life. CDEC discussed that post–COVID-19 condition is not within the scope of this recommendation and there is no evidence available to inform any recommendation on the use of nirmatrelvir-ritonavir for the treatment of post–COVID-19 condition.

Background

COVID-19 is an illness caused by SARS-CoV-2. The rapid global spread of the virus led to a pandemic, as declared by WHO on March 11, 2020. In Canada, as of August 19, 2023, the cumulative count of documented COVID-19 cases has reached 4,706,450; however, serologic data suggest that approximately 80% of the population contracted the infection at some point. The cumulative death toll since the beginning of the pandemic stands at 53,345.

Patients with COVID-19 exhibit a broad spectrum of symptoms, varying from mild in the majority of cases (e.g., fever and malaise) to occasionally severe hypoxia with acute respiratory distress syndrome. In some patients, mild to moderate COVID-19 can lead to severe medical complications or progress into severe or critical states that are associated with a high morbidity and mortality rate.

Several risk factors have been involved in the progression to severe COVID-19. Earlier in the pandemic, a wide range of risk factors were identified, which included older age, cardiovascular disease, diabetes mellitus, hypertension, cerebrovascular disease, dementia, neurodevelopmental disorders, and chronic kidney disease. At the time of this review, the relevance of these risk factors for progressing to severe disease was not the same as it was during the pandemic; as population immunity was building over time, the proportion and characteristics of patients being hospitalized due to COVID-19 were also changing. The 2 clinical experts consulted by CADTH for this review agreed that, currently, the most relevant risk factors to progress to severe COVID-19 are older age (> 80 years), frailty, underprotection from SARS-CoV-2 (patients unvaccinated and who did not have a prior infection), and severe immunosuppression. This would encompass a larger population of patients than recommendations from the recently updated WHO living guideline, which state that patients at high risk of hospitalization are those with diagnosed immunodeficiency syndromes, patients who have undergone solid organ transplant and receive immunosuppressants, as well as patients with
autoimmune illness receiving immunosuppressants. The guideline indicates that patients in the high-risk category have a 6% rate of hospitalization. The guideline also highlights characteristics which are now associated with only a moderate risk of progressing to severe disease, a category of patients who have a 3% rate of hospitalization: patients older than 65 years, patients living with obesity, with diabetes and/or chronic cardiopulmonary disease, with chronic kidney or liver disease, have active cancer, with disabilities, and those with comorbidities of chronic disease.

Nirmatrelvir-ritonavir has been approved by Health Canada for “the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.” The recommended dosage is 300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100-mg tablet) with all 3 tablets taken together orally twice daily for 5 days. Nirmatrelvir-ritonavir should be administered as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of symptom onset. For patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m² to < 60 mL/min/1.73 m²), the dosage of nirmatrelvir-ritonavir is reduced to 150 mg of nirmatrelvir (one 150-mg tablet) and 100 mg ritonavir (one 100-mg tablet) twice daily for 5 days. Nirmatrelvir-ritonavir is not recommended in patients with severe renal impairment (eGFR < 30 mL/min).

Sources of Information Used by the Committee
To make its recommendation, the committee considered the following information:

- a review of 1 double-blind, randomized controlled trial (RCT) (EPIC-HR) in adult outpatients with symptoms of mild to moderate COVID-19 who were not vaccinated against SARS-CoV-2 and who were considered at high risk for progression to severe disease and/or hospitalization
- patients’ perspectives gathered by patient groups, Arthritis Consumer Experts, the Canadian Breast Cancer Network, the Gastrointestinal Society, the Lung Health Foundation, the Save Your Skin Foundation, the Sickle Cell Awareness Group of Ontario, and the International Federation on Ageing
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with COVID-19
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the request for reconsideration (described subsequently).

Stakeholder Perspectives

Patient Input
Patient input was submitted by 7 patient groups: Arthritis Consumer Experts, the Canadian Breast Cancer Network, the Gastrointestinal Society, the Lung Health Foundation, the Save Your Skin Foundation, the Sickle Cell Awareness Group of Ontario, and the International Federation on Ageing.
The inputs were mostly gathered directly from patients through online surveys, focus groups, or by email. Most patients represented by the patient groups highlighted that, because of their condition, they were at higher risk of worse outcomes from COVID-19 than the general population, and that COVID-19 complications also posed a risk of worsening their baseline condition. Several patients described serious symptoms from contracting COVID-19 and shared their experience with the use of nirmatrelvir-ritonavir. Preventing hospitalizations was highlighted as a main goal of treatment. One patient group focused on the need to have treatment options for post–COVID-19 condition. The patient groups highlighted that nirmatrelvir-ritonavir needs to be safe, effective, and accessible on uniform terms and conditions across the country. Indeed, some reported that the administrative process required for approval can be lengthy, and the criterion for eligibility varies by jurisdiction, with some enforcing stricter parameters for access.

**Clinician Input**

**Input From Clinical Experts Consulted by CADTH**

The current treatment paradigm for mild to moderate COVID-19 in Canada is to prevent hospitalization or death among patients at high risk for these outcomes. Risk factors for hospitalization and death can be determined from control groups in observational studies or from provincial outcomes data. Typically, age older than 80 years, unvaccinated status, and multiple comorbidities leading to frailty are considered the main risk factors. In addition, patients who have severe immunosuppression, and those with a prior disease trajectory of worsening in the first 5 days or not starting to improve within 5 days, have a high likelihood of hospitalization. However, provincial outcome data show that, even in the highest risk subgroups, the hospitalization rate remains low, averaging 2.5%.

SARS-CoV-2 has evolved significantly since the beginning of the pandemic, and the current risk of hospitalization or death is very low. Therefore, most cases of mild to moderate COVID-19 require no specific treatment; symptoms are typically mild and self-limited. First-line therapy for the vast majority of the population with COVID-19 infection is supportive care. If required to prevent hospitalization, benefits of treatment must be balanced against the risks and adverse events (AEs), including drug-drug interactions that jeopardize patient well-being.

Nirmatrelvir-ritonavir is the first and only approved oral treatment in Canada, available through an emergency use authorization. One of the main caveats of the pivotal trial informing approval is that it was performed when the delta SARS-CoV-2 variant was dominant. Ongoing clinical trials are currently being performed; when the results become available, these trials may provide evidence on the use of nirmatrelvir-ritonavir in other variants of SARS-CoV-2. In the meantime, additional evidence is available in the form of observational studies; however, their use to inform policy-making has limitations.

The role of nirmatrelvir-ritonavir in the long term is likely to evolve around the small number of individuals who are highly compromised and remain at high risk of negative outcomes because of a failure to fight infection or physiologic frailty. Treatment must be based on a positive diagnostic test because many viral upper respiratory tract infections present similarly, and nirmatrelvir-ritonavir can cause significant and potentially dangerous drug-drug interactions.
Nirmatrelvir-ritonavir should ideally be prescribed in primary care by a clinician who is able to evaluate symptoms, disease trajectory, and risk for progression. This could be either a generalist clinician or a specialist in relevant fields for patients with high-risk conditions (e.g., oncologist, rheumatologist). To offer easy and rapid access, some jurisdictions use a decentralized model (no designated prescribers, availability through any participating pharmacy), whereas some permit pharmacists to make the prescription. In the current stage of the pandemic, clinical experts suggest reevaluating whether there is still a need for such decentralized models, including pharmacist prescriptions, accompanied with a shift toward better selection and identification of patients who are likely to benefit the most from treatment.

**Drug Program Input**

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for nirmatrelvir-ritonavir:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

<table>
<thead>
<tr>
<th>Implementation issues</th>
<th>Response</th>
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<tbody>
<tr>
<td>Relevant comparators</td>
<td>The clinical experts noted to CDEC that the use of remdesivir is severely limited in outpatients because of its IV administration. However, they mentioned that it could be used in a very small population of patients who already have an IV access.</td>
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<tr>
<td>Remdesivir is indicated for the same patient population and is generally used as a</td>
<td>The clinical experts indicated that there are advantages and disadvantages to both centralized and decentralized models, and that it is the prerogative of each jurisdiction to decide what model works best for them. A centralized model is likely to offer more control of use according to the appropriate criteria and surveillance data, whereas a decentralized model is likely to offer rapid and easy access to the drug for patients. CDEC noted that there is no clear optimal implementation approach with variable geographic and population-level factors and suggested that jurisdictions should carry on with whatever model works best for them.</td>
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<td>second-line treatment for patients who cannot take nirmatrelvir-ritonavir due to</td>
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<td>contraindication or drug interaction. In addition to contraindication or drug</td>
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<td>interaction to nirmatrelvir-ritonavir, is there any other scenario where you would</td>
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<td>use remdesivir instead of nirmatrelvir-ritonavir?</td>
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<td>Some jurisdictions use a centralized access model (centralized intake with designated</td>
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<td>prescribers and dispensing pharmacies) while other provinces use a decentralized</td>
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<td>model (no designated prescribers, availability through any participating pharmacy).</td>
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<tr>
<td>Additionally, some jurisdictions permit pharmacists to prescribe nirmatrelvir-</td>
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<td>ritonavir. In your opinion, which model should be used?</td>
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### Implementation issues

<table>
<thead>
<tr>
<th>Eligibility criteria for the pivotal trial required patients to have all of the following:</th>
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<tbody>
<tr>
<td>• confirmed SARS-CoV-2 infection</td>
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<tr>
<td>• symptom onset no more than 5 days before randomization</td>
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<tr>
<td>• at least 1 sign or symptom of COVID-19 on the day of randomization</td>
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<tr>
<td>• at least 1 characteristic or coexisting condition associated with high risk of progression to severe COVID-19.</td>
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The US FDA has removed the positive viral test requirement from the indication, which could open access to many individuals who do not actually have COVID-19.

• Would all of the above criteria from the pivotal trial be appropriate for reimbursement purposes?

• If applicable, how should “confirmed SARS-CoV-2 infection” be determined?

### Response

CDEC agreed with the clinical experts that, based on clinical evidence, most of the risk factors for progressing to severe disease that were used in trials performed earlier during the pandemic are not relevant at the time of this recommendation. The 2 clinical experts consulted by CADTH for this review agreed that the most relevant risk factors are currently older age (> 80 years), frailty, underprotection from SARS-CoV-2 (patients who are unvaccinated and who did not have a prior infection), and severe immunosuppression. The trajectory of the disease would also be important to consider (e.g., whether patients’ conditions are getting worse, experience during prior infections).

CDEC recommended that nirmatrelvir-ritonavir be reimbursed for severely or moderately immunosuppressed individuals.

CDEC agreed with the clinical experts there needs to be a positive viral test result to ensure the patient is infected with SARS-CoV-2. There was no consensus among the experts about whether it should be via rapid testing or PCR. However, they noted that self-administered COVID-19 tests have been widely accessible and are convenient to use.

### Considerations for initiation of therapy

<table>
<thead>
<tr>
<th>How should “high risk of progression to severe COVID-19” be defined to maximize safety and cost-effectiveness?</th>
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<tr>
<td>The 2 clinical experts consulted by CADTH for this review agreed that the most relevant risk factors are currently older age (&gt; 80 years), frailty, underprotection from SARS-CoV-2 (patients who are unvaccinated and who did not have a prior infection), and severe immunosuppression. The trajectory of the disease would also be important to consider (e.g., whether patients are getting worse, experience during prior infections). However, the clinical experts noted to CDEC that these risk factors may not be associated with clinical benefits from treatment with nirmatrelvir-ritonavir in contemporary management of COVID-19.</td>
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CDEC recommended that nirmatrelvir-ritonavir be reimbursed for severely or moderately immunosuppressed individuals because these patients were considered to benefit the most from a treatment with nirmatrelvir-ritonavir based on more recent evidence from observational studies.

### How soon after receiving a course of nirmatrelvir-ritonavir should individuals be eligible to receive another course if they are reinfected and/or have relapse?

The clinical experts noted to CDEC that there is no evidence at this time to inform this question, but noted that they might consider re-treatment with nirmatrelvir-ritonavir in patients who are severely immunocompromised who are reinfected, and noted that each time a patient is infected with SARS-CoV-2, the antibody response increases and protection increases, and the risk of hospitalization and death decreases. Therefore, in theory, a second infection is less severe than a primary infection.
## Implementation issues

**Vaccinated individuals were excluded from the pivotal study; however, some real-world evidence confirms benefits of nirmatrelvir-ritonavir in these individuals. Should vaccinated patients be eligible to receive nirmatrelvir-ritonavir?**

The clinical experts discussed this issue; however, there is only limited evidence at this time to inform this question. The clinical experts felt that vaccination status should not be a criterion for receiving nirmatrelvir-ritonavir, but rather the criteria should focus on other risk factors. CDEC recommended that nirmatrelvir-ritonavir be reimbursed for individuals who have severe or moderate immunosuppression regardless of their vaccination status.

## Considerations for prescribing of therapy

The National Institutes of Health guidelines do not officially recommend extending nirmatrelvir-ritonavir treatment beyond 5 days but acknowledge that some prescribers may choose to prolong treatment duration for certain patients (i.e., patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication).

- Are there patients who would benefit from extended (e.g., 10-day) treatment?

CDEC agreed with the clinical experts that the 5-day treatment course would be used in almost all patients. One expert noted that the 10-day course may be considered for patients at extreme risk who are expected to have very poor outcomes. There may be a niche use for patients who are chronically infected, although the data are limited to case reports and series so no firm conclusions can be made.

## Generalizability

- **Should nirmatrelvir-ritonavir be used for prophylaxis of COVID-19 in any outbreak settings?**

  CDEC and the clinical experts agreed that nirmatrelvir-ritonavir should not be used as prophylaxis for COVID-19.

- **Should nirmatrelvir-ritonavir be prescribed for patients planning to travel out of country so that it can be taken in the event of illness while travelling?**

  CDEC and the clinical experts agreed that nirmatrelvir-ritonavir should not be prescribed for patients planning to travel out of country.

## Care provision issues

- **Nirmatrelvir-ritonavir has the potential to cause significant, life-threatening drug interactions. Many sources of information on drug interactions are available to help prescribers determine whether nirmatrelvir-ritonavir is appropriate for their patients and how to mitigate significant interactions with other drugs.**

  This was a comment from the drug programs to inform CDEC deliberations.

- **Patients on drug therapies that interact with nirmatrelvir-ritonavir (e.g., solid organ transplant patients on calcineurin inhibitors) may require active drug concentration monitoring if nirmatrelvir-ritonavir is administered.**

  This was a comment from the drug programs to inform CDEC deliberations.

## System and economic issues

- **Given that nirmatrelvir-ritonavir has a limited treatment window, some jurisdictions may not be able to implement restrictive criteria and still ensure timely access to the drug, given how provincial adjudication systems are designed. This will be a larger issue if the cost and/or utilization is high, and restrictive criteria are required to ensure appropriate use. Do you have any advice for jurisdictions that would not be able to implement any proposed criteria and still ensure timely access to therapy?**

  The clinical experts provided insights at the prescriber level about how to grant effective access to the drug through family physicians and other health care professionals, such as pharmacists. However, CDEC agreed with the clinical experts that they could not advise on issues surrounding the internal adjudication process from drug plans.

CDEC = Canadian Drug Expert Committee; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.
Clinical Evidence

Systematic Review

Description of Studies
One multicentre, double-blind RCT was the primary source of evidence for the efficacy and safety of nirmatrelvir-ritonavir. The EPIC-HR trial (N = 2,246) evaluated the comparative efficacy and safety of nirmatrelvir-ritonavir to placebo for the treatment of adult outpatients with symptoms of mild to moderate COVID-19 who were not vaccinated against SARS-CoV-2 and who were considered at high risk for progression to severe disease and/or hospitalization at the time the study was performed based on a wide range of prespecified patient characteristics. The primary outcome of the EPIC-HR trial was a combined outcome of the proportion of patients with COVID-19–related hospitalization or who died from any cause through day 28.

Efficacy Results
Nirmatrelvir-ritonavir reduced the incidence of COVID-19–related hospitalization or death from any cause through day 28 compared with placebo. In the overall population of patients treated as per the product monograph (within 5 days of symptoms onset), the absolute reduction was −5.62% (95% CI, −7.21% to −4.03%; P < 0.001). The proportions of patients experiencing a primary outcome event (0.9% with treatment and 6.3% with placebo) show that the incidence of COVID-19–related hospitalization or death from any cause in the EPIC-HR population was low. Overall, the magnitude of effect with nirmatrelvir-ritonavir was considered relatively small. In 1 subgroup analysis performed in patients aged 65 years and older, nirmatrelvir-ritonavir reduced the primary outcome incidence by −13.9% compared with placebo (modified intention-to-treat1 population = 0.8%; placebo = 14.6%; 95% CI, −20.1 to −7.8; P < 0001), suggesting there are subgroups of patients in whom the treatment effect is more pronounced, especially in the presence of a higher risk of worst outcomes. However, the use of nirmatrelvir-ritonavir in the EPIC-HR trial did not yield clinically meaningful differences compared with placebo on outcomes assessing duration or severity of COVID-19 signs and symptoms.

Harms Results
Nirmatrelvir-ritonavir was relatively well tolerated by patients in the EPIC-HR trial. Similar proportions of patients experienced AEs between treatment groups; however, numerically more patients in the placebo group reported AEs of higher severity and serious AEs than in the treatment group. Discontinuation of treatment due to AEs was low. No patients died in the nirmatrelvir-ritonavir group and 15 patients (1.3%) died in the placebo group; most reasons were related to COVID-19.

There is a lack of evidence on the safety of nirmatrelvir-ritonavir, especially in patients who are older and/or frail, who may be at increased risk of experiencing more harms outcomes. Of note, the use of nirmatrelvir-ritonavir is associated with CYP3A inhibition, which can result in a number of drug-drug interactions. Patients with significant drug-drug interactions were excluded from the EPIC-HR trial.
Critical Appraisal
The overall risk of bias in the EPIC-HR trial was low. However, the most significant issue with the EPIC-HR trial is that the findings of the trial cannot be generalized to the patient population living in Canada who are at high risk for progression to severe COVID-19, as defined in clinical practice at the time of this review. Patients included in the EPIC-HR trial were relatively young, which limits conclusions about the efficacy and safety of nirmatrelvir-ritonavir in an older population, who are considered at increased risk. As per the study's selection criteria, EPIC-HR did not include vaccinated patients or patients who had COVID-19 in the past. This is an important gap because, according to the most recent data, at least 80% of the Canadian population completed a primary series of COVID-19 vaccination, and approximately 80% of the population has contracted a SARS-CoV-2 infection at some point. Patients included in the study presented with various comorbidities. At the time the trial was performed, these were considered risk factors for severe illness from COVID-19; however, these concomitant conditions in themselves are no longer considered to significantly increase the risk of worst outcomes. The 2 clinical experts consulted by CADTH for this review agreed that the current most relevant risk factors for progressing to severe disease and hospitalization are older age (> 80 years), frailty, underprotection from SARS-CoV-2 (patients who are unvaccinated and those who have not had a prior infection), and severe immunosuppression.

In addition to the population issues, the primary variant observed in the trial population was delta. However, this SARS-CoV-2 variant was no longer circulating at the time of this review; the main variant of concern was omicron and its subsequent subvariant, which are substantially less virulent.

Studies Addressing Gaps in the Evidence From the Systematic Review
Observational studies were submitted by the sponsor and reviewed by CADTH to bridge the evidence gaps from the EPIC-HR trial. CADTH also considered a prior Health Technology Review of nirmatrelvir-ritonavir for the treatment of COVID-19. With the help of clinical experts, observational studies within the report were selected and described for populations particularly relevant to Canadian clinical practice. As part of the overall body of evidence, their findings can inform decision-making regarding the optimal use of nirmatrelvir-ritonavir in specific populations of real-life patients who would be considered more vulnerable to COVID-19 worst outcomes and who could not be included in the pivotal EPIC-HR RCT. Overall, 1 additional RCT and 6 observational cohort studies contributed to the evidence.

EPIC-SR
EPIC-SR (N = 1,153) was a multicentre, double-blind, placebo-controlled RCT comparing nirmatrelvir-ritonavir to placebo for the treatment of adult patients with symptoms of COVID-19 who were not hospitalized and who were at low risk of progression to severe illness, which is outside of the Health Canada indication for nirmatrelvir-ritonavir. Patients were excluded if they had an underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (unless the patient was vaccinated) or a prior COVID-19 infection. A subgroup of patients who were vaccinated who had at least 1 risk factor for severe COVID-19 (n = 721) was submitted by the sponsor as evidence for the efficacy of nirmatrelvir-ritonavir in
patients who were vaccinated during the omicron wave. Enrolment was terminated early due to very low rates of hospitalization and death observed. The EPIC-SR trial did not meet its primary objective; it failed to demonstrate a difference between nirmatrelvir-ritonavir and placebo on COVID-19–related hospitalizations or deaths from any cause, as well as on the primary outcome of time to sustained alleviation of all targeted COVID-19 signs and symptoms in both the overall population of patients at standard risk of progressing to severe disease and in a subgroup of patients with an underlying medical condition who were vaccinated. Therefore, the EPIC-SR trial is not informative with respect to the evidence gaps.

Lewnard et al. (2023)
A study by Lewnard et al. (n = 7,274 treated with nirmatrelvir-ritonavir; n = 126,152 not treated with nirmatrelvir-ritonavir) was a retrospective cohort study using a matched cohort framework conducted in California. Patients were included if they were aged at least 12 years, enrolled in the Kaiser Permanente Southern California health plans, and had a positive SARS-CoV-2 polymerase chain reaction (PCR) result between April 8 and October 7, 2022. The primary end point of this study was hospital admission or death from any cause within 30 days. The included population was mostly vaccinated, with characteristics that were consistent with standard risk of progressing to severe COVID-19. The study resulted in patients treated with nirmatrelvir-ritonavir having clinically similar hospitalization and mortality rates compared to patients who did not receive this treatment. The Lewnard et al. study has limited impact in addressing gaps in the evidence, mainly due to the presence of substantial confounding effects and because the included population did not have the characteristics of patients currently considered at high risk for progressing to severe COVID-19.

Schwartz et al. (2023)
A study by Schwartz et al. (n = 8,876 treated with nirmatrelvir-ritonavir; n = 168,669 not treated with nirmatrelvir-ritonavir) was a population-based cohort study with propensity score–derived inverse probability of treatment weighting conducted in Ontario. Patients were included in the study if they were Ontario residents aged between 18 and 110 years who had a positive PCR test for SARS-CoV-2 between April 4, 2022, and August 31, 2022. The Schwartz et al. (2023) study included age, sex, number of doses of SARS-CoV-2 vaccine, previous SARS-CoV-2 infection, time from last vaccine dose, and high versus standard risk using the definition from the Ontario COVID-19 Science Advisory Table. Patients who received nirmatrelvir-ritonavir were highly vaccinated (85% had received at least 3 doses of SARS-CoV-2 vaccine); 42% of these patients were considered at high risk for progressing to severe disease. Overall, 2.1% of patients who received nirmatrelvir-ritonavir had a hospital admission due to COVID-19 or an all-cause death within 30 days compared with 3.7% for patients who did not receive this treatment. The weighted odds ratio was 0.56 (95% CI, 0.47 to 0.67) and the number needed to treat (NNT) to prevent 1 case of severe COVID-19 was 62 (95% CI, 44 to 77). This suggests statistically significant but clinically small effectiveness of nirmatrelvir-ritonavir in a real-life population. The study by Schwartz et al. may inform gaps in the evidence for the efficacy of nirmatrelvir-ritonavir in patients who were vaccinated during an omicron wave, especially because it was performed in a population living in Canada; however, this was not consistent with current definitions of high risk for progressing to severe COVID-19. In the study, the impact of nirmatrelvir-ritonavir to prevent hospitalization and death was considered modest. Because of potential issues with selection
and confounding, findings should be interpreted with caution due to uncertainty surrounding the true treatment effect.

**Kaboré et al. (2023)**
A study by Kaboré et al. (n = 8,402 treated with nirmatrelvir-ritonavir; n = 8,402 not treated with nirmatrelvir-ritonavir) was a retrospective cohort study conducted in Quebec that used nearest-neighbour propensity score matching. Patients were included if they were covered by the Quebec public health insurance plan in 2022 and had either a prescription for nirmatrelvir-ritonavir (treated group) or a positive SARS-CoV-2 PCR result (control group) between March 15 and October 15, 2022. The study showed a benefit of nirmatrelvir-ritonavir compared to no such treatment on the primary outcome of COVID-19–related hospitalizations within 30 days (3.6% in the nirmatrelvir-ritonavir treatment group versus 11.5% in the control group; RR = 0.31; 95% CI, 0.28 to 0.36; P < 0.001). This yielded an NNT of 13, as calculated by CADTH. The magnitude of the treatment effect observed with nirmatrelvir-ritonavir on preventing hospitalization should be interpreted with caution because the natural incidence of COVID-19–related hospitalizations in the control group was higher than would be expected in clinical practice; the estimates may have been affected by confounding factors, resulting in bias in favour of treatment with nirmatrelvir-ritonavir. The study by Kaboré et al. may inform on subpopulations who are more likely to benefit from treatment. According to subgroup analyses, the magnitude of the treatment effect was greater in unvaccinated patients than in the overall population and was also greater in patients aged 70 years and older (versus younger than 70 years) and in patients whose last vaccine dose was before the previous 6 months (versus within the previous 6 months). Results also favoured nirmatrelvir-ritonavir versus no such treatment in a subgroup of patients who were severely immunocompromised.

**Dryden-Peterson et al. (2023)**
A study by Dryden-Peterson et al. (n = 12,541 treated with nirmatrelvir-ritonavir; n = 32,010 not treated with nirmatrelvir-ritonavir) was a population-based cohort study using inverse probability-weighted analysis performed in the US. The study was assessed as having a moderate risk of bias. Patients were included if they were 50 years and older and had a COVID-19 diagnosis between January 1 and July 17, 2022. Patients who received nirmatrelvir-ritonavir were highly vaccinated (79% vaccinated and boosted), half of the population was aged at least 65 years, 36% of patients were immunocompromised, and 23% had a solid tumour. The study showed a small benefit of treatment with nirmatrelvir-ritonavir compared to no such treatment on the primary outcome of hospitalization within 14 days or death within 28 days (0.5% versus 0.9%, respectively; absolute risk difference = −0.4%; RR = 0.56; 95% CI, 0.42 to 0.75). This yielded an NNT of 250, as calculated by CADTH. Findings were consistent across subgroups; however, vaccination status affected the magnitude of treatment effect, which was higher in patients who were not fully vaccinated (NNT of 50 as calculated by CADTH) or whose last vaccine was more than 20 weeks before the study (NNT of 196 as calculated by CADTH).

**Dormuth et al. (2023)**
A study by Dormuth et al. (n = 3,433 treated with nirmatrelvir-ritonavir; n = 3,433 not treated with nirmatrelvir-ritonavir) was a retrospective cohort study of patients at increased vulnerability to complications from
COVID-19 infection conducted in British Columbia. Inclusion of this study was suggested by the clinical experts due to the high representativity of the population and its sound methodology. High dimensional propensity score models were used to minimize confounding and the nearest-neighbour method was used for matching patients. The study was performed between February 1, 2022, and February 3, 2023. The study assessed the effect of nirmatrelvir-ritonavir on death from any cause and COVID-19–related hospitalizations compared to no such treatment in different cohorts of patients who were clinically extremely vulnerable and at high risk for complications from COVID-19:

- cohort 1 — patients aged at least 18 years and severely immunocompromised
- cohort 2 — patients aged at least 18 years and moderately immunocompromised
- cohort 3 — patients with selected medical conditions (severe respiratory disorders, insulin-dependent diabetes, or certain blood disorders, metabolic disorders, and cancers not captured in other groups)
- expanded eligibility — patients at lower risk than clinically extremely vulnerable but at higher risk than the general population.

Hospitalization rates were low and aligned with clinical practice; in spite of this, patients who were severely immunocompromised (cohort 1) and received nirmatrelvir-ritonavir had a −2.5% absolute risk difference (95% CI, −4.8 to −0.2) of experiencing the primary outcome compared to those in the control group, yielding an NNT of 40. The risk difference was −1.7% (95% CI, −2.9 to −0.5) for patients who were moderately immunocompromised (cohort 2) and −1.3% (95% CI, −2.8 to 0.1) for patients with selected medical conditions (cohort 3), yielding NNTs of 60 and 75, respectively.

**Hedvat et al. (2022)**

A study by Hedvat et al. (n = 28 treated with nirmatrelvir-ritonavir; n = 75 not treated with nirmatrelvir-ritonavir) was a retrospective study of just adult patients who were solid organ transplant recipients and had a positive SARS-CoV-2 PCR test within a research hospital in New York City between December 16, 2021, and January 19, 2022. The study was assessed as having a moderate risk of bias. The use of nirmatrelvir-ritonavir was associated with a reduction in the incidence of hospitalization or death from any cause compared with no treatment (14.3% versus 33.3%, respectively; adjusted risk ratio for organ transplant type of 0.21; 95% CI 0.06, 0.71; NNT of 6 as calculated by CADTH) and in hospitalization or death from COVID-19 (10.7% versus 30.7%, respectively; adjusted risk ratio for organ transplant type of 0.17; 95% CI, 0.04 to 0.67; NNT of 5 as calculated by CADTH). According to the clinical experts consulted by CADTH, hospitalization rates in this study were higher than those seen in clinical practice in similar populations with organ transplants. Therefore, although the findings are consistent with the known vulnerability of this patient group, generalizability of the findings are uncertain.

**Discussion of Evidence Gaps**

Findings from the observational studies can inform decision-making regarding the optimal use of nirmatrelvir-ritonavir in specific populations of patients who would be considered more vulnerable to worst outcomes of COVID-19 and who were not included in the pivotal EPIC-HR RCT.
Results from 5 observational studies discussed in this review show that nirmatrelvir-ritonavir is effective compared to no such treatment against the prevalent omicron SARS-CoV-2 variant of concern in high-risk populations.

Observational studies also suggest that the effectiveness of nirmatrelvir-ritonavir in high-risk populations, as clinically defined in Canadian clinical practice, is likely to vary among the various categories of populations:

- In 2 studies with subgroup analyses according to age group, there was a greater magnitude of effect with nirmatrelvir-ritonavir treatment versus no treatment in patients aged at least 70 years compared with patients who were younger than 70 years. The overall incidence of hospitalization was also greater in both treatment and control groups in patients who were in the older age group.

- In 3 studies in which the population consisted of patients who were highly vaccinated and in subgroup analyses of patients who had received prior vaccination, nirmatrelvir-ritonavir was associated with a smaller magnitude of treatment effect overall compared to patients who were not vaccinated. In these studies or subgroup analyses, the incidence of hospitalization was typically small for both the treatment and control arms, as would be expected in clinical practice, suggesting that patients who are vaccinated have a lower risk overall of progressing to severe COVID-19 regardless of whether they received treatment with nirmatrelvir-ritonavir.

- In 2 studies that included patients who were severely and/or moderately immunocompromised, treatment with nirmatrelvir-ritonavir was effective in preventing hospitalizations and deaths compared with no such treatment, although the magnitude of effect varied across the studies. In a large observational study in Canada, the magnitude of the treatment effect was proportional to the level of immunosuppression; it was at its highest in the cohort of patients who were severely immunocompromised.

Issues were noted in the observational studies regarding selection and confounding; this introduces uncertainty about the true treatment effect. Although the findings should be interpreted with caution, they are part of the overall body of evidence and remain informative regarding the optimal use of nirmatrelvir-ritonavir in clinical practice.

### Economic Evidence

#### Table 3: Cost and Cost-Effectiveness

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of economic evaluation</td>
<td>Cost-utility analysis&lt;br&gt;Decision tree followed by Markov model</td>
</tr>
<tr>
<td>Target population</td>
<td>Adult patients 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</td>
</tr>
<tr>
<td>Treatment</td>
<td>Nirmatrelvir-ritonavir</td>
</tr>
<tr>
<td>Dose regimen</td>
<td>150 or 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days</td>
</tr>
</tbody>
</table>
**Component** | **Description**
--- | ---
Submitted price | $1,288.88 per 5-day treatment course, consisting of either:
- 20 × 150 mg nirmatrelvir tablets and 10 × 100 mg ritonavir tablets
- 10 × 150 mg nirmatrelvir tablets and 10 × 100 mg ritonavir tablets

Treatment cost | $1,288.88 per 5-day course

Comparator | Standard of care basket comparator comprising over-the-counter and off-label steroid medications

Perspective | Canadian publicly funded health care payer

Outcomes | QALYs, life-years

Time horizon | 10 years

Key data source | EPIC-HR, a phase II/III, double-blind, placebo-controlled randomized controlled trial in adult patients with a confirmed diagnosis of SARS-CoV-2 infection who were symptomatic but not hospitalized

Key limitations
- The population studied in the EPIC-HR trial does not accurately reflect the population at risk for progression to severe COVID-19 today. This is due to higher vaccination rates and the dominance of the SARS-CoV-2 omicron variant, which was not present at the time of EPIC-HR. These differences represent a fundamental challenge in interpreting the results from the sponsor’s submitted evidence dossier and the accompanying pharmacoeconomic model which were based on EPIC-HR.
- CADTH identified and corrected a programming error in the sponsor’s model. The sponsor’s results presented here reflect this correction.

CADTH reanalysis results
- To better represent the population at risk for progression to severe COVID-19, CADTH used efficacy data from an observational study provided by the sponsor, conducted in a highly vaccinated population in Ontario.
- In the CADTH base case, the ICER for nirmatrelvir-ritonavir was $442,082 per QALY gained compared to standard of care (incremental costs: $897; incremental QALYs: 0.002). A price of $494 per treatment course (reduction of approximately 62%) would be required for nirmatrelvir-ritonavir to be considered cost-effective at a $50,000 per QALY gained threshold.
- When considering the number needed to treat to avoid a severe case of COVID-19 (hospitalization or death), based on the study by Schwartz et al. (2023), 62 individuals who are at high risk would need to be treated. When comparing the drug acquisition costs of nirmatrelvir-ritonavir for 62 individuals (approximately $80,000) with the cost of a general ward admission to treat COVID-19 ($20,000), a price reduction of approximately 75% would be required to ensure minimal financial impact to health care systems.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

**Budget Impact**

The budget impact of nirmatrelvir-ritonavir is highly dependent on the population of patients who will be eligible to receive it. The sponsor estimated that the budget impact of nirmatrelvir-ritonavir for the treatment of COVID-19 in adult patients at high risk for progression was $247,088,096 in year 1, $261,040,638 in year 2, and $275,333,908 in year 3, for a 3-year total of $783,462,642.

CADTH noted that a number of aspects could change this estimate: the size of the eligible population — should use be restricted to patients who are at higher risk of requiring hospitalization for COVID-19; the proportion of patients seeking treatment, which could be lower as testing for COVID-19 becomes less prevalent and available and individuals no longer seek treatment; and the symptomatic COVID-19 infection rate. When the eligible population is revised to align with clinical experts’ recommendation on the

Due to market share assumptions, the budget impact is directly proportional to the population size. CADTH notes uncertainty in the proportion of patients seeking treatment and the symptomatic infection rate, which were explored in scenario analyses.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for nirmatrelvir-ritonavir for “the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.” In their request, the sponsor identified the following issues:

- Assessment of risk factors for progression to severe COVID-19 — Age and comorbidities were not considered risk factors by CDEC. Other risk-related issues excluded from Table 1 (of this recommendation) are the definition for adequately vaccinated and the elevated risk associated with congregate care settings for older adults.
- Issues of transparency and reporting of the economic evaluation — The ICER of $442,082 per QALY obtained by the CADTH reanalysis using the efficacy estimate from the Schwartz et al. study cannot be reproduced using the submitted model.
- Interpretation of the benefits of nirmatrelvir-ritonavir — While immunocompromised populations described in Table 1 (of this recommendation) will likely benefit the most from nirmatrelvir-ritonavir treatment, the sponsor strongly disagrees that the available evidence demonstrates that they are the only population that would benefit from treatment.

In the meeting to discuss the sponsor’s request for reconsideration, CDEC considered the following information:

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 2 clinical specialist with expertise in the diagnosis and treating of patients with COVID-19
- feedback from the public drug plans
- feedback from 1 clinician group, the Nova Scotia Emerging and Re-emerging Infections Therapeutics and Prophylactics Recommendations Group
- feedback from 5 patient groups, the Canadian Breast Cancer Network, the Gastrointestinal Society, Save Your Skin Foundation, Sickle Cell Awareness Group of Ontario, and Asthma Canada.
All stakeholder feedback received in response to the draft recommendation is available on the CADTH website.

CDEC Information

**Initial Meeting Date: December 20, 2023**

**Members of the Committee**
Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Regrets:** None

**Conflicts of interest:** None

**Reconsideration Meeting Date: March 28, 2024**

**Members of the Committee**
Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

**Regrets:** 2 expert committee members did not attend

**Conflicts of interest:** None