CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	January 2024
Report Length:	16 Pages

Single Technology

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that nirmatrelvir-ritonavir be reimbursed 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 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 Schwartz et al., which enrolled patients from Ontario, and Dormuth et al., which enrolled patients from British Columbia, which 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 found that the effectiveness of nirmatrelvir-ritonavir is considerably reduced in the general population who are adequately vaccinated, in younger patients, and in patients who were not immunocompromised. Where in Dormuth et al., when compared to patients who did not receive nirmatrelvir-ritonavir, treatment with nirmatrelvir-ritonavir was associated with statistically significant relative reductions in prevention of death or admission to hospital in the severely immunocompromised patients (risk difference [RD], −2.5%, 95% CI, −4.8% to −0.2%) and the moderately immunocompromised patients (RD, −1.7%; 95% CI, −2.9% to −0.5%). Two other patient groups were assessed in Dormuth et al., one of which considered the group of patients who were not immunocompromised but had medical conditions associated with a high risk for complications from COVID-19 and the other group consisted of patients who were at lower risk of COVID-19–related complications than the previous groups, but who had risk factors that put them at higher risk of complications, in both of these patient groups there were no statistically significant difference between those 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. Given that patients who are at high risk for progression to severe COVID-19 often live with an existing acute or chronic condition(s), patients also expressed the need for a treatment that does not present contraindications with their current medicines 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 Schwartz et al., as Dormuth et al., 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 ICER was likely closer to $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

Reimbursement condition	Reason	Implementation guidance
Initiation		
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 any of the following: 1.1. severely immunosuppressed due to one or more of the conditions: • Solid organ transplant recipients • Treated for malignant hematologic condition • Bone marrow, stem cell transplant or transplant-related immunosuppressant use • Receipt of an Anti-CD20 agents or B-cell depleting agents (such as rituximab) in the previous 2 years • Severe primary immunodeficiencies 1.2. moderately immunosuppressed due to one or more of the conditions: • Treatment for cancer including solid tumors • Significantly immunosuppressing drugs (e.g., biologic in the last three months, oral immune suppressing medication in the last months, oral steroid [20mg/day of prednisone equivalent taken on an ongoing basis] in the last month, or immune-suppressing infusion or injection in the last three months). • Advanced untreated HIV infection or treated HIV[a]	Definition for severely immune suppressed and moderately immune suppressed was used by Dormuth et al., where a statistically significant benefit was seen in the primary composite endpoint of death from any cause and COVID-19–related hospitalization.[b]	CDEC noted that the Health Canada indication note that nirmatrelvir-ritonavir should be initiated as soon as possible after a diagnosis of COVID-19 based on a positive test has been made, and within 5 days of symptom onset which may be an implementation challenge in jurisdictions which no longer provide routine outpatient testing.

Reimbursement condition	Reason	Implementation guidance
• Moderate primary immunodeficiencies • Renal conditions (i.e., hemodialysis, peritoneal dialysis, glomerulonephritis and dispensing of a steroid, eGFR<15mL/min)		
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 alone. A price reduction of at least 62% would be required for nirmatrelvir-ritonavir to be able 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.	
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.	—

COVID-19 = coronavirus disease 2019; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; NNT = number needed to treat; QALY = quality-adjusted life year.

[a] Presence of a diagnosis code (2 MSP or 1 DAD/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^3 or CD4 fraction ≤ 15% at any time.

[b] 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;6(10):e2336678. doi:10.1001/jamanetworkopen.2023.36678

Discussion Points

- CDEC recognized that patients who are at increased risk for severe COVID-19 need access to treatments that are effective against COVID-19. As individuals who have a higher risk for severe COVID-19 often live with an existing acute or chronic condition(s), patients need a variety of treatments that do not present contraindications with their current medicines and therapies. In addition, patients need treatments that are effective against different variants of COVID-19.
- CDEC discussed the practical implications of lack of testing for COVID-19 outside of a hospital setting to confirm a positive results of SARS-CoV-2 viral testing case, however testing outside of a hospital setting but may not be available in all jurisdictions. CDEC also noted that some jurisdictions have established infrastructure for testing and prescribing. However, to ensure timely accessibility, and consideration of testing and treating and accessibility, jurisdictions might need to implement test and treat strategies that are timely and accessible, and equitable. This may require a substantial investment in Rapid antigen test (RAT) kits deployment to patients who are at high risk for progression to severe COVID-19.
- CDEC discussed that there is a lack of evidence on the safety of nirmatrelvir-ritonavir, especially in elderly and frail patients who may also be taking other medications and therefore at higher risk for significant drug interactions.
- 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 and included older age, cardiovascular disease, diabetes mellitus, hypertension, cerebrovascular disease, dementia, neurodevelopmental disorders, and chronic kidney disease. CDEC 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, the proportion and characteristics of patients being hospitalized or dying due to COVID-19 have evolved.

- CDEC discussed that tesults from the pivotal phase 3 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, specifically, 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, different circulating strains with differing virulence (delta vs. omicron) and exclusion of patients with prior infection or vaccination.
- 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 the viral evolution.
- Patients with Long COVID (patients infected with the virus that causes COVID-19 and experience long-term effects from their infection beyond the acute infection) expressed a need for a therapy that can cure their condition, which 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 Long COVID 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 Long COVID.

Background

Coronavirus disease 2019 (COVID-19) is an illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The rapid global spread of the virus led to a pandemic, as declared by the World Health Organization (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 which 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 and 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 is not the same as it was during the pandemic; as population immunity has been building up over time, the proportion and characteristics of patients being hospitalized due to COVID-19 are now changing. The two 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. Those 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 over the age of 65 years, patients with obesity, diabetes and/or chronic cardiopulmonary disease, chronic kidney or liver disease, and active cancer, as well as patients 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 three tablets taken together orally twice daily for 5 days. Nirmatrelvir-ritonavir should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of symptom onset. In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dosage of nirmatrelvir-ritonavir 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 one double-blind, randomized controlled trial (EPIC-HR) in adult symptomatic outpatients with 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

Stakeholder Perspectives

Patient Input

Patient input was submitted by seven 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 worst outcome 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 long covid. 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-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 above 70, unvaccinated status and multiple comorbidities leading to frailty are considered the main risk factors. In addition, severely immunosuppressed patients, and those with a prior disease trajectory of worsening in the first five 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%.

The SARS-CoV-2 virus has evolved significantly since the beginning of the pandemic, and the current risk of hospitalization or death is very low. Therefore, the vast majority of mild to moderate COVID-19 requires no specific treatment, symptoms being 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, including drug-drug interactions that jeopardize patient well-being.

Nirmatrelvir-ritonavir is the first and only approved oral treatment in Canada, through an emergency use authorization. One of the main caveats of the pivotal trial informing approval is that it was performed at a time when the Delta SARS-CoV-2 variant was circulating. Ongoing clinical trials are currently being performed; when 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 highly compromised individuals who 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 since 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 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). In order to offer easy and rapid access, some jurisdictions use a decentralized model (no designated prescribers, availability through any participating pharmacy), while some permit pharmacists to make the prescription. In the current stage of the pandemic, clinical experts suggested reevaluating whether there is still a need for such decentralized models, including pharmacist prescription, with a shift towards 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

Implementation issues	Response
Relevant comparators	
Remdesivir is indicated for the same patient population and is generally used as a second-line treatment for patients who cannot take nirmatrelvir-ritonavir due to contraindication or drug interaction. In addition to contraindication or drug interaction to nirmatrelvir-ritonavir, is there any other scenario where you would use Remdesivir instead of nirmatrelvir-ritonavir?	The clinical experts noted to CDEC that the use of remdesivir is severely limited in outpatients by its IV administration. They mentioned that it could be used however in a very small population of patients who already have an IV access.
Some jurisdictions use a centralized access model (centralized intake with designated prescribers and dispensing pharmacies) while other provinces use a decentralized model (no designated prescribers, availability through any participating pharmacy). Additionally, some jurisdictions permit pharmacists to prescribe nirmatrelvir-ritonavir. In your opinion, which model should be used?	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, while 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 geographic and population-level factors variable and suggested that jurisdictions should carry on with whatever

Implementation issues	Response
	implementation approach has been chosen for their individual jurisdictions.
Considerations for initiation of therapy	
Eligibility criteria for the pivotal trial required patients to have: • confirmed SARS-CoV-2 infection; • symptom onset no more than 5 days before randomization; • at least one sign or symptom of COVID-19 on the day of randomization; and • at least one characteristic or coexisting condition associated with high risk of progression to severe COVID-19 The U.S. FDA has removed the positive viral test requirement from the indication, which could open access to many individuals who don't actually have COVID-19. a) Would all of the above criteria from the pivotal trial be appropriate for reimbursement purposes? b) If applicable, how should "confirmed SARS-CoV-2 infection" be determined?	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 two 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 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, what happened during prior infections). CDEC recommended that nirmatrelvir-ritonavir be reimbursed for severely or moderately immunesuppressed. CDEC agreed with the clinical experts the need to have a positive viral test result for ensuring that the patient is infected with SARS-CoV-2. There was no consensus among the experts as to whether it should be rapid testing or PCR. They noted however that self-administered COVID-19 tests have been widely accessible and convenient to use.
How should "high risk of progression to severe COVID-19" be defined in order to maximize safety and cost-effectiveness?	The two 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 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, what happened during prior infections). However, the clinical experts noted to CDED that these risk factors may not be associated with clinical benefits from taking nirmatrelvir-ritonavir in comtemporary management of COVID-19. CDEC recommended that nirmatrelvir-ritonavir be reimbursed for severely or moderately immunesuppressed, as 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 retreatment with nirmatrelvir-ritonavir in patients who are severely immunocompromised who get reinfected, and noted that each time patient get infected with COVID-19 the anti body response increases, and protection and increases, and the risk of hospitalization and death decreases, and that in theory a second COVID-19 infection is less severe than primary COVID-19 infection.
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 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

Implementation issues	Response
	receiving nirmatrelvir-ritonavir, but rather the criteria should focus on other risk factors. CDEC recommended that nirmatrelvir-ritonavir be reimbursed for severely or moderately immunesuppressed, regardless of the 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 virtually 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 for the prophylaxis of 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 wouldn't be able to implement any proposed criteria and still ensure timely access to therapy?	The clinical experts provided insights at the prescriber level, as to how to grant effective access to the drug through family physicians and other healthcare 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.

COVID-19 = coronavirus disease 2019; FDA = Food and Drug Administration; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

Clinical Evidence

Systematic Review

Description of Studies

One multicentre, double-blind (DB), randomized controlled trial (DB RCT) was the primary source of evidence for the efficacy and safety of nirmatrelvir-ritonavir. EPIC-HR (N = 2,246) evaluated the superiority of nirmatrelvir-ritonavir compared with placebo for the treatment of adult symptomatic outpatients with 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 EPIC-HR 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 control) 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 overall relatively small. In one subgroup analysis performed in patients 65 years of age and older, nirmatrelvir-ritonavir reduced the primary outcome incidence by -13.9% compared with placebo (mITT1 population, 0.8% versus 14.6%, respectively; 95% CI -20.1, -7.8; p<0001), suggesting that there might be subgroups of patients where the treatment effect is more pronounced, especially in the presence of a higher risk of worst outcomes. The use of nirmatrelvir-ritonavir in EPIC-HR however 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 in EPIC-HR. Similar proportions of patients experienced AEs between treatment groups; however, numerically more patients reported AEs of higher severity and SAEs in the placebo group than in the treatment group. Discontinuation of treatment due to AEs was low. No patient died in the nirmatrelvir-ritonavir and 15 patient (1.3%) in the placebo group died, most reasons being related to COVID-19.

There is a lack of evidence on the safety of nirmatrelvir-ritonavir, especially in elderly and frail patients, who may be at increased risk of experiencing harms outcomes. Of note, the use of nirmatrelvir-ritonavir is associated with CYP3A inhibition, resulting in a number of drug-drug interactions; patients with significant drug-drug interactions were excluded from EPIC-HR.

The safety of nirmatrelvir-ritonavir was not assessed in observational studies.

Critical Appraisal

The overall risk of bias for EPIC-HR was low.

However, the most significant issue with EPIC-HR is that the findings of the trial cannot be generalized to the Canadian population of patients 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, limiting conclusions on the efficacy and safety of nirmatrelvir-ritonavir in an elderly population, who is 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 since according to the most recent data, at least 80% of the Canadian population completed a primary series of COVID-19 vaccine, and approximately 80% of the population has contracted a SARS-CoV-2 infection at some point.[2] Finally, patients included in the study presented with various comorbidities which, at the time the trial was performed, were considered risk factors for severe illness from COVID-19; however, these concomitant conditions in themselves are not considered to increase significantly the risk of worst outcomes anymore. The two clinical experts consulted by CADTH for this review agreed that the most relevant risk factors for progressing to severe disease and hospitalization are currently older age (>80 years), frailty, under-protection from SARS-CoV-2 (patients unvaccinated and those who do not have 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 is not circulating anymore at the time of this review, as the main variant of concern is 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 in order to bridge the evidence gaps from EPIC-HR. CADTH also considered a prior Health Technology Review of Nirmatrelvir-ritonavir for the Treatment of COVID-19 (a copy of which is provided in Appendix 2). With the help of clinical experts, observational studies within the report were selected and described in

details below, for which the populations were 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 RCT EPIC-HR. Overall, one additional RCT and six observational cohort studies contributed to the evidence.

EPIC-SR

EPIC-SR (n = 1,153) was a multicenter DB placebo-controlled RCT comparing nirmatrelvir-ritonavir to placebo for the treatment of non-hospitalized, symptomatic, adult patients with COVID-19 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 vaccinated patients with at least one risk factor for severe COVID-19 (n = 721) was submitted by the sponsor as evidence for the efficacy of nirmatrelvir-ritonavir in vaccinated patients during the Omicron wave. Enrollment was early terminated due to a very low rate of hospitalization or death observed. EPIC-SR did not meet its primary objective, failing to demonstrate a difference between nirmatrelvir-ritonavir and placebo on COVID-19-related hospitalization or death 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, EPIC-SR is not informative with regard to the evidence gaps.

Lewnard et al.

Lewnard et al. 2023 (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 performed in California, US. Patients were included if they were aged at least 12 years, enrolled in the Kaiser Permanente Southern California (KPSC) health plans, and had a positive SARS-CoV-2 PCR result between April 8 and October 7, 2022. The primary endpoint 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 nirmatrelvir-ritonavir treated patients having a clinically similar hospitalization / mortality rate compared to patients who did not receive this treatment. Lewnard et al. has limited impact in addressing gaps in the evidence, mainly due to the presence of substantial confounding and to the included population not having the characteristics of patients currently considered at high-risk for progressing to severe COVID-19.

Schwartz et al.

Schwartz et al. 2023 (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 performed in Ontario, Canada. 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. Patients who received nirmatrelvir-ritonavir were highly vaccinated (85% had received at least 3 doses of SARS-CoV-2 vaccine); 42% 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 all-cause death within 30 days, compared with 3.7% for patients who did not receive this treatment, resulting in a weighted OR of 0.56 (95% CI, 0.47 to 0.67) and a number needed to treat to prevent one case of severe COVID-19 (NNT) of 62 (95% CI 44 to 77). This suggests a statistically significant but clinically small effectiveness of nirmatrelvir-ritonavir in a real-life population. Schwartz et al. may inform gaps in the evidence for the efficacy of nirmatrelvir-ritonavir in vaccinated patients during an Omicron wave, especially as it was performed in a Canadian population, which was however not consistent with current definitions for 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 however be interpreted with caution, as there is uncertainty surrounding the true treatment effect.

Kaboré et al.

Kaboré et al. 2023 (n = 8,402 treated with nirmatrelvir-ritonavir; n = 8,402 not treated with nirmatrelvir-ritonavir) was a retrospective cohort study using nearest-neighbor propensity score matching performed in Québec, Canada. 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 of 0.31 (95% CI, 0.28, 0.36); p<0.001). This yielded a NNT of 13, as calculated by CADTH. The magnitude of treatment effect observed with nirmatrelvir-ritonavir on preventing hospitalization should however be interpreted with caution, as 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. Kaboré et al. may inform on subpopulations who are more likely to benefit from treatment. According to subgroup analyses, the magnitude of treatment effect was greater in unvaccinated patients than in the overall population, and was also greater in patients 70 years and older (versus younger than 70 years) and in patients whose last vaccine dose was before the prior 6 months (versus within prior 6 months). Results also favoured nirmatrelvir-ritonavir versus no such treatment in a subgroup of severely immunocompromised patients.

Dryden-Peterson et al.

Dryden-Peterson et al. 2023 (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 Massachusetts and southern New Hampshire, US. The study was assessed as having a moderate risk of bias (Appendix 2). 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 at least 65 years of age, 36% of patients were immunocompromised and 23% had a solid tumour. The study showed a small benefit of 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 of -0.4%; RR of 0.56; 95% CI 0.42, 0.75). This yielded a 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 prior to the study (NNT of 196 as calculated by CADTH).

Dormuth et al.

Dormuth et al. 2023 (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 performed in British Columbia, Canada. Inclusion of this study was suggested by clinical experts, due to the high representativity of the population and sound methodology. High dimensional propensity score models were used to minimize confounding and the nearest neighbor method was used for matching patients. The study was performed between February 1, 2022, and February 3, 2023. The study assessed the effectiveness of nirmatrelvir-ritonavir on death from any cause and COVID-19–related hospitalization compared to no such treatment in different cohorts of clinically extremely vulnerable (CEV) patients at high risk for complications from COVID-19, as follows:
CEV1: at least 18 years and severely immunocompromised;
CEV2: at least 18 years and moderately immunocompromised;
CEV3: 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 (EXEL): patients at lower risk than CEV but at higher risk than general population.

Hospitalization rates were low and aligned with clinical practice; in spite of this, severely immunocompromised patients (CEV1 cohort) who received nirmatrelvir-ritonavir had a -2.5% absolute risk difference (95% CI -4.8, -0.2) of experiencing the primary outcome compared to control, yielding a NNT of 40. The corresponding risk difference was -1.7% (95% CI -2.9, -0.5) for moderately immunocompromised patients (CEV2 cohort) and -1.3% (95% CI-2.8, 0.1) for patients with selected medical conditions (CEV3 cohort), yielding NNTs of 60 and 75, respectively.

Hedvat et al.

Hedvat et al. 2022 (n = 28 treated with nirmatrelvir-ritonavir; n = 75 not treated with nirmatrelvir-ritonavir) was a retrospective study of all adult patients who were solid organ transplant recipients and who had a positive SARS- CoV- 2 PCR test within the research hospital between December 16, 2021 and January 19, 2022. The study was performed in New York City, US, and was assessed as

having a moderate risk of bias (Appendix 2). The use of nirmatrelvir-ritonavir was associated with a reduction, compared with no treatment, in the incidence of hospitalization or death from any cause (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 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, 0.67; NNT of 5 as calculated by CADTH). According to the clinical experts consulted by CADTH, hospitalization rates in this study were however higher than what is 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 for the observational studies 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 RCT EPIC-HR.

Results from five observational studies discussed in this review show that nirmatrelvir-ritonavir is effective compared to no such treatments against the prevalent Omicron SARS-CoV-2 variant of concern among 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 amongst the various categories of populations:

- In two studies with subgroup analyses according to age group, there was a greater magnitude of effect with nirmatrelvir-ritonavir treatment versus no treatment in patients at least 70 years of age, compared with patients who were less than 70 years. The overall incidence of hospitalization was also greater in both treatment and control groups in patients with older age.
- In three studies where the population consisted of highly vaccinated patients and in subgroups analyses of patients who received prior vaccination, nirmatrelvir-ritonavir was overall associated a smaller magnitude of treatment effect when compared to vaccinated patients. In these studies or subgroup analyses, the incidence of hospitalization was typically small for both treatment and control arms, as would be expected in clinical practice, suggesting that vaccinated patients have overall a lower risk of progressing to severe COVID-19, no matter whether or not they received treatment.
- In two studies that included severely and/or moderately immunocompromised patients, nirmatrelvir-ritonavir was effective in preventing hospitalization and death compared with no such treatment; the magnitude of effect varied across the studies. In a large Canadian, observational study, the magnitude of treatment effect was proportional to the level of immunosuppression, being at its highest in the severely immunocompromised cohort.

Issues were noted in the observational studies with selection and confounding; this introduces uncertainty around the true treatment effect, which was addressed in a varying level through the weighting models and use of covariates. Though findings should be interpretated with caution, as part of the overall body of evidence, they remain informative regarding the optimal use of nirmatrelvir-ritonavir in clinical practice.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Adult patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID, including hospitalization or death
Treatment	Nirmatrelvir-ritonavir
Dose regimen	150 or 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days
Submitted price	$1,288.88 per 5-day treatment course, consisting either of: • 20 × 150 mg nirmatrelvir tablets and 10 × 100 mg ritonavir tablets; or, • 10 × 150 mg nirmatrelvir tablets and 10 × 100 mg ritonavir tablets
Treatment cost	$1,288.88 per 5-day course

Component	Description
Comparator	Standard of care (SoC) basket comparator comprising over-the-counter and off-label steroid medications
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	10 years
Key data source	EPIC-HR, a phase II/III double blind, placebo-controlled randomized controlled trial in non-hospitalized symptomatic adult patients with a confirmed diagnosis of SARS-CoV-2 infection
Key limitations	• The population studied in the EPIC-HR trial does not accurately reflect the population at risk for progression to severe COVID today. This is due to higher vaccination rates and the advent of the Omicron variant of COVID, 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 accompanying pharmacoeconomic model which are 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, 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 SOC (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 (NNT) to avoid a severe case of COVID (hospitalization or death), based on the study by Schwartz et al. (2023) 62 high risk individuals would need to be treated. When comparing the drug acquisition costs of nirmatrelvir-ritonavir for 62 individuals (~$80,000) with the cost of a general ward admission to treat COVID ($20,000), a price reduction of approximately 75% would be required to ensure minimal financial impact to the health care system.

Budget Impact

The budget impact of nirmatrelvir-ritonavir is highly dependent on the population that will be eligible to receive it. The sponsor estimated that the budget impact of nirmatrelvir-ritonavir for the treatment of COVID 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 three-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; the proportion of patients seeking treatment – which could be lower as testing for COVID becomes less prevalent and available, and individuals no longer seek treatment; the symptomatic COVID infection rate. When the eligible population is revised to align with clinical experts' recommendation on the appropriate use of nirmatrelvir-ritonavir, CADTH estimates the three-year budget impact to the public drug plans of introducing nirmatrelvir-ritonavir for the treatment of COVID to be $397,148,534 (year 1: $125,207,708, year 2: $132,323,111, year 3: $139,617,714).

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.

CDEC Information

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.

Meeting date: December 20, 2023

Regrets:

None

Conflicts of interest:

None