



CADTH Reimbursement Recommendation

Remdesivir (Veklury)

Indication: For the treatment of coronavirus disease 2019 in nonhospitalized adults and pediatric patients (weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization and death

Sponsor: Gilead Sciences Canada, Inc.

Final recommendation: Reimburse with conditions



Summary

What Is the CADTH Reimbursement Recommendation for Veklury?

CADTH recommends that Veklury be reimbursed by public drug plans for the treatment of COVID-19 in adults who are not hospitalized and have 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 and death, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Veklury should only be covered to treat patients who meet the criteria used by each of the public drug programs for reimbursement of Paxlovid for the treatment of COVID-19 in adults. Treatment should be initiated as soon as possible and within 7 days of symptom onset.

What Are the Conditions for Reimbursement?

Veklury should only be reimbursed if treatment does not exceed 3 days, is not used in combination with any other antiviral medication for COVID-19 (including Paxlovid), and the cost is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that patients with COVID-19 who were considered to be at high risk for progression to severe disease but were not hospitalized could benefit from Veklury for preventing hospitalization. There is uncertainty about whether these findings reflect the actual benefits of Veklury because the trial took place before omicron (B.1.1.529) was the main circulating variant, the patients in the trial were unvaccinated, and they were enrolled based on a definition of high risk that no longer meets the current definition used by clinicians today.
- Veklury may meet patients' unmet needs by reducing the risk of severe disease leading to hospitalization in those with moderate to severe immune suppression who are, therefore, at risk of complications from progressing to severe COVID-19. However, it is uncertain what impact Veklury has on mortality based on the trial results. Veklury may also address patients' need for a COVID-19 treatment that does not present contraindications with their current medication.
- Based on CADTH's assessment of the health economic evidence, Veklury does not represent good value to the health care system at the public list price. A price reduction is therefore required.



Summary

- Based on public list prices, Veklury is estimated to cost the public drug plans approximately \$3.4 million over the next 3 years; however, this depends on the number of COVID-19 cases and the uptake of Veklury.

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 that affect progression to severe disease have evolved over time. Population immunity has increased, and the number and characteristics of patients hospitalized because of COVID-19 have changed. According to a November 2023 WHO living guideline, patients at high risk of serious complications, including those with a compromised immune system, have an estimated 6% hospitalization rate.

Unmet Needs in COVID-19

The patient group expressed a need for access to treatments that are effective at reducing the risk of severe disease and death caused by the currently circulating COVID-19 variants. Patients also expressed the need for a treatment that does not have contraindications with their current medications.

How Much Does Veklury Cost?

Treatment with Veklury is expected to cost approximately \$2,642 per 3-day course.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that remdesivir be reimbursed for the treatment of COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are not hospitalized but are at high risk for progression to severe COVID-19, including hospitalization and 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. Patients also highlighted the importance of treatments that do not have contraindications with their current medications.

CDEC also considered that the clinical impact of COVID-19, the patient population at risk, and the management landscape has evolved over time. In 1 double-blind, randomized controlled trial (RCT) in patients 12 years or older (weighing at least 40 kg) with confirmed SARS-CoV-2 infection who were not hospitalized and who were considered to be at high risk for progression to severe COVID-19 (the PINETREE trial), remdesivir was associated with a statistically significant reduction in COVID-19–related hospitalizations by day 28; however, there were no deaths in the study to inform the effect of treatment on mortality. The hazard ratio (HR) for the remdesivir group versus the placebo group was 0.13 (95% confidence interval [CI], 0.03 to 0.59; $P = 0.0076$). Although patients residing in a skilled nursing facility and patients with an immunocompromised status were relevant populations, no patients from either subgroup experienced a COVID-19–related hospitalization or death from any cause by day 28 so the results were not informative for clinical decision-making in these groups. Remdesivir was also associated with numerically fewer COVID-19–related medically attended visits (MAVs). There were insufficient data to draw conclusions on the effect of remdesivir on oxygen supplementation, intensive care unit (ICU) admissions, and mechanical ventilation outcomes. The PINETREE trial took place before omicron (B.1.1.529) was the main circulating variant of SARS-CoV-2, patients in the trial were unvaccinated, and they were enrolled based on a definition of high risk that no longer meets the current definition used in clinical practice today, per the clinical expert. Therefore, it would be reasonable to expect that the estimate of treatment effect would be smaller today than what was observed in the trial. One prospective cohort study (Rajme-Lopez et al., 2022) in patients who were immunosuppressed, vaccinated, and at high risk for COVID-19 progression demonstrated that remdesivir resulted in fewer all-cause hospitalizations compared to no remdesivir (adjusted HR = 0.16; 95% CI, 0.06 to 0.44) early in the period when omicron became the dominant circulating variant.

The patient input received for this review expressed a need for COVID-19 treatments that are effective in preventing progression to severe COVID-19, including hospitalization or death, effective against newer COVID-19 variants, and do not present contraindications with their current medications and therapies. CDEC noted that remdesivir could potentially address some of these needs in patients at high risk for progression to severe COVID-19, such as those with moderate to severe immune suppression, who are not hospitalized.

Using the sponsor-submitted price for remdesivir, the incremental cost-effectiveness ratio as estimated by CADTH for remdesivir was \$390,996 per quality-adjusted life-year gained compared with standard of care to treat COVID-19 in adults and pediatric patients who are at high risk for progression to severe COVID-19 but are not hospitalized. A price reduction would be required for remdesivir to achieve an incremental cost-effectiveness ratio of \$50,000 per quality-adjusted life-year gained. There is uncertainty in the estimation of the price reduction because of the limitations in the clinical evidence base.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for remdesivir should be based on the criteria used by each of the public drug programs for reimbursement of nirmatrelvir-ritonavir for the treatment of COVID-19 in adults.	<p>There is insufficient evidence that remdesivir is clinically superior or inferior to nirmatrelvir-ritonavir, which is currently reimbursed for COVID-19.</p> <p>Clinical guidelines and expert opinion indicate that IV remdesivir is an alternative option for patients who have contraindications and potential drug-drug interactions with nirmatrelvir-ritonavir, though the latter is generally preferred because of its oral format and the practical administrative challenges with IV remdesivir.</p>	<p>CDEC noted that the Health Canada indication states that remdesivir 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 7 days of symptom onset, which may be an implementation challenge in jurisdictions where routine outpatient testing is no longer provided.</p> <p>CDEC also noted the challenges associated with accessing an infusion clinic for IV administration and postinfusion monitoring (though at-home nursing care may be an option), as well as the administrative challenges for hospitals and clinics for the 3-day treatment duration.</p> <p>CDEC noted that for adults, public drug programs may consider reimbursing remdesivir in patients who cannot receive nirmatrelvir-ritonavir because of contraindications with their current medications.</p>
Prescribing		
2. The duration of treatment with remdesivir should not exceed 3 days.	<p>Patients enrolled in the PINETREE trial and the cohort study (Rajme-Lopez et al. 2022) received remdesivir for 3 days. CDEC also noted that there is no evidence available for the use of remdesivir for more than 3 days in patients who are not hospitalized.</p>	—
3. Remdesivir is not to be used in combination with any other antiviral medication for COVID-19, including nirmatrelvir-ritonavir.	<p>There is no evidence to determine the effects of remdesivir when used in combination with other antiviral medications for COVID-19.</p>	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
4. A reduction in price	The cost-effectiveness of remdesivir is highly uncertain. CADTH undertook an analysis that estimated the ICER for remdesivir to be \$390,996 per QALY gained when compared with standard of care alone. A price reduction of at least 82% would be required for remdesivir to achieve an ICER of \$50,000 per QALY gained.	—
Feasibility of adoption		
5. The feasibility of adoption of remdesivir must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

CDEC = Canadian Drug Expert Committee; ICER = incremental cost-effectiveness ratio; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; RAT = rapid antigen test.

Discussion Points

- CDEC discussed the unmet need for patients who cannot receive nirmatrelvir-ritonavir because of contraindications with their current medications. CDEC noted that remdesivir could potentially address that need in patients who are not hospitalized but are at high risk for progression to severe COVID-19, such as those with moderate to severe immune suppression.
- Given that remdesivir is administered by IV infusion for a duration of 3 days, CDEC discussed the implementation challenges associated with accessing an infusion clinic for IV administration and postinfusion monitoring, as well as the administrative challenges for hospitals and clinics for the 3-day treatment duration, especially in terms of providing equitable access for patients across the country.
- Recognition of the risk factors involved in 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 from COVID-19 have evolved.
- CDEC discussed that the definition of high risk for progression to severe disease has narrowed over time. According to the literature and the clinical expert, the most important risk factors for

progression include lack of SARS-CoV-2 immunity, severe immune suppression, multiple chronic comorbidities, and older age (e.g., 80 years and older). The patients considered the highest risk are those who cannot produce a sufficient immune response to clear the infection and therefore may be more likely to benefit from an antiviral drug. It should also be noted that those who are at high risk of severe disease are not necessarily the same as those who derive the most benefit from treatment and it will be important for future research to confirm that these 2 populations overlap. In its deliberations, CDEC considered the evidence available and its relevance to the real-world disease context.

- 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), they 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 discussed that results from the pivotal phase III trial (PINETREE) were not informative in determining the efficacy of remdesivir in contemporary COVID-19 infection in Canada because of the study's external validity limitations. These included that the population enrolled in the PINETREE trial does not represent the population at risk for severe COVID-19 infection in 2024 because of 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, and patients with prior vaccination were excluded.
- 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 remdesivir for the treatment of post-COVID-19 condition.
- CDEC noted that in the PINETREE trial, few patients in both the remdesivir and placebo groups reported symptom alleviation based on the InFLUenza Patient-Reported Outcome (FLU-PRO) Plus questionnaire and that the outcome was hindered by missing data.
- Although the Health Canada indication includes the treatment for pediatric patients, CDEC noted that there was limited evidence for the use of remdesivir in adolescent patients with COVID-19 who are not hospitalized, as only 5 patients in the group of those aged 12 to 18 years received remdesivir in the PINETREE trial, and no adolescent patients were enrolled in the cohort study (Rajme-Lopez et al., 2022). In addition, the clinical expert stated that it would be rare to treat young individuals with remdesivir; hence, CDEC recommended not to reimburse remdesivir in adolescent patients with COVID-19 who are not hospitalized.

Background

COVID-19 is an illness caused by SARS-CoV-2 in which most current cases of infection present with absent or mild symptoms, though some patients can have severe symptoms. WHO has estimated the mortality risk for patients with nonsevere disease to be less than 1%, regardless of hospitalization risk level. According to the literature and the clinical expert consulted by CADTH, the most important risk factors for progression

to severe disease include lack of SARS-CoV-2 immunity, severe immune suppression, multiple chronic comorbidities, and older age (e.g., 80 years and older). The omicron variant of concern has surpassed others in terms of transmissibility, shorter incubation period, and being associated with reduced morbidity and mortality.

Based on serology, it is estimated that more than 99% of people living in Canada has some form of infection-acquired or vaccine-induced immunity to the virus. Most patients with COVID-19 can be managed at home through symptomatic care, monitoring for clinical deterioration, and isolation to prevent transmission. The need for additional treatment is based on a patient's severity of illness and risk level of progressing to severe disease, the assessments of which vary across jurisdictions. According to the Association of Medical Microbiology and Infectious Disease Canada (AMMI) updated recommendations, nirmatrelvir-ritonavir and remdesivir may be considered in patients with mild disease (i.e., those who do not require oxygen supplementation) based on the patient's risk, severity, and trajectory of symptoms. The WHO guidelines for COVID-19 therapeutics provide a conditional recommendation for the use of remdesivir to treat patients with nonsevere disease who are at high risk of hospitalization, acknowledging the challenges with IV administration. Other factors to consider when deciding which treatment to use include local availability of therapies, duration of symptoms, feasibility of administration, and potential drug interactions.

Remdesivir has been approved by Health Canada for the treatment of COVID-19 in adults and pediatric patients (weighing at least 40 kg) who have positive results of direct SARS-CoV-2 viral testing, are not hospitalized, and are at high risk for progression to severe COVID-19, including hospitalization and death. For this CADTH review, the sponsor has requested reimbursement of remdesivir for the treatment of COVID-19 in patients who are not hospitalized, are 12 years of age or older (weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and are at high risk for progression to severe COVID-19, including hospitalization and death. Remdesivir is a nucleotide prodrug that incorporates into nascent viral ribonucleic acid and inhibits viral replication by prematurely terminating ribonucleic acid transcription. It is available as a single loading dose of 200 mg on day 1 and a 100 mg dose on days 2 and 3 for patients who are not hospitalized.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, double-blind RCT in patients aged 12 years and older with at least 1 preexisting risk factor for progression to hospitalization or 60 years and older, regardless of the presence of other preexisting risk factors; and 1 real-world evidence study included to address gaps in the evidence
- patients' perspectives gathered by 1 patient group, Gastrointestinal Society
- input from public drug programs that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with COVID-19

- input from 2 clinician groups, British Columbia Transplant Clinicians and Ontario Health Infectious Diseases Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

One group, the Gastrointestinal Society, responded to CADTH's call for patient group input by gathering information through meetings and discussions with health care professionals, researchers, academics, and first-hand experiences among staff affected by COVID-19. According to the patient group, SARS-CoV-2 infection causes damage of the intestinal lining, leading to irritating and sometimes severe symptoms, and modifies the microbiome in the gastrointestinal tract, which can leave a patient more susceptible to opportunistic infections. The patient group stated that because of possible reinfection and recurrent illness, the availability of effective vaccines and treatments remains paramount. It was emphasized that despite the available options to protect patients from severe disease or death, treatments are difficult to access and there is concern around contraindications with current medications.

Clinician Input

Input From Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH stated that the aim of treatment for patients with SARS-CoV-2 infection who are not hospitalized is to avoid hospitalization, death, and disability. While most patients will improve without intervention, the expert indicated that the 2 key criteria for identifying patients who could receive remdesivir for COVID-19 are having a high-risk underlying medical condition and showing evidence of substantial symptoms. Although there are fewer administrative challenges with nirmatrelvir-ritonavir compared to remdesivir, the latter would be an alternative option for patients who cannot receive nirmatrelvir-ritonavir because of intolerance and drug-drug interactions. According to the clinical expert, the evidence supporting the claim that either drug reduces post-COVID-19 condition is inconclusive, especially in immune populations, and this topic is subject to ongoing research. The expert indicated that between the 2 options, nirmatrelvir-ritonavir is generally preferred for patients who do not have a contraindication.

According to the expert, few patients are likely to benefit from treatment for COVID-19 and it is only those with severe immune suppression who are more likely to benefit. Moreover, these patients tend to already be receiving specialty care and can be identified as high risk based on their underlying illness. The expert emphasized that specific viral testing is necessary to differentiate SARS-CoV-2 infection from other influenzalike illnesses and for access to treatment.

More recently, fewer patients are being admitted to the hospital for COVID-19 because of mild disease trajectory, and ICU admissions are rare. However, patients who are severely immunocompromised (e.g., those with B-cell depletion) are unable to effectively clear viral infections and may develop chronic infection. The expert identified these patients as being of great concern for progression to severe disease.

There are no clinical markers for assessing patients with mild disease, though medical intervention should be pursued in those who continue to worsen. Per the expert, commonly used clinical trial outcomes (e.g., hospitalization, ICU admissions, and death) are also important in practice. Remdesivir for patients who are not hospitalized is indicated for a set 3-day duration and it is expected that most patients will complete treatment.

Given that remdesivir is an IV medication, a team of health care providers who can insert, care for, and remove an IV is necessary for administration. The care team is also required for monitoring the patient during infusion and assessing potential infection at the IV site. The expert stated that treatment typically takes place at hospitals or infusion clinics, though at-home nursing care may be an option for some.

Clinician Group Input

Two clinician groups, British Columbia Transplant Clinicians (7 authors) and Ontario Health Infectious Diseases Advisory Committee (4 authors), responded to CADTH's call for clinician group input. Both clinician groups indicated that the goals of treatment include reducing COVID-19–related mortality, hospitalizations, ICU admissions, and symptom severity; preventing progression to severe disease and long-term sequelae; and accelerating recovery. The groups highlighted the ongoing need for treatments and vaccines with evidence of long-term safety and efficacy, as well as drug options that improve convenience of administration. Timely access to testing and COVID-19 treatments (considering the narrow time frames for initiating therapy) were noted as ongoing issues.

The groups noted that nirmatrelvir-ritonavir is not often used in patients in whom interactions between the drug and their current medications cannot be safely managed and, in such cases, remdesivir may be used where contraindications to nirmatrelvir-ritonavir exist or in those who are outside the 5-day initiation window for nirmatrelvir-ritonavir. British Columbia currently recommends and has prioritized remdesivir for patients with symptoms who have received solid organ transplants, but are not hospitalized, regardless of vaccine status or previous infection, while the Ontario clinician group noted that older age, immunocompromised status, nonvaccinated status, presence of multiple and/or uncontrolled comorbidities, and specific medical or social vulnerabilities are considerations when assessing greater need for intervention. Those who are asymptomatic or beyond the 7-day onset would be least suited to receive remdesivir.

According to the clinician group in British Columbia, patients with solid organ transplant receiving outpatient remdesivir are monitored by infusion clinic nurses during the 3-day treatment course and are followed up by their respective transplant centres. The clinician group in Ontario indicated that, in general, a specialist is not required for managing patients receiving remdesivir and that the drug can be administered in a community setting (e.g., long-term care homes), hospital outpatient clinic, or hospital emergency department. Both groups noted that a clinically meaningful response would be a significant reduction in hospitalizations, ICU

admissions, and deaths; no need for new or increased supplemental oxygen; and symptom resolution or improvement. Discontinuation of therapy should be considered in patients with adverse events (AEs), such as increased serum creatinine, increased serum liver enzymes, and hypersensitivity or infusion reactions, or if new data indicate that viral variants are no longer susceptible to remdesivir.

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 remdesivir:

- considerations for initiation of therapy
- considerations for prescribing of therapy.

The clinical expert 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
Considerations for initiation of therapy	
<p>Eligibility criteria for the pivotal trial included all of the following:</p> <ul style="list-style-type: none"> • confirmed SARS-CoV-2 infection • aged ≥ 18 years, or aged ≥ 12 and < 18 years and weighing ≥ 40 kg, with ≥ 1 preexisting risk factor for progression to hospitalization • age ≥ 60 years, regardless of other preexisting risk factors • ≥ 1 symptom consistent with COVID-19 for ≤ 7 days • not receiving, requiring, or expecting to require supplemental oxygen • not requiring hospitalization (i.e., > 24 hours of acute care). <p>Patients were excluded based on the following:</p> <ul style="list-style-type: none"> • prior hospitalization for COVID-19 • other treatments for COVID-19, including vaccines • elevated ALT or AST (≥ 5 times the ULN) • low eGFR (< 30 mL/min/1.73 m²). <p>Are the eligibility criteria from the pivotal trial appropriate as reimbursement criteria for this indication?</p> <p>How should “confirmed SARS-CoV-2 infection” be determined?</p> <p>How would “preexisting risk factor for progression to hospitalization” be defined (i.e., are the preexisting risk factors outlined in the eligibility criteria for the pivotal trial still relevant)?</p>	<p>The clinical expert and CDEC agreed that because of changes in population immunity and virus pathogenicity, the eligibility criteria for the PINETREE trial would not be appropriate as reimbursement criteria for remdesivir. CDEC recommended the criteria for reimbursement of remdesivir be based on the criteria used by each of the public drug programs for reimbursement of nirmatrelvir-ritonavir for the treatment of COVID-19 in adults.</p> <p>The clinical expert and CDEC agreed that it is essential that patients with symptoms who are to receive remdesivir have confirmed SARS-CoV-2 infection. The expert indicated any approved test is acceptable (though a PCR test is preferred) and that patients who attend an infusion setting may be able to better access PCR testing.</p> <p>The clinical expert and CDEC agreed that the preexisting risk factors included in the PINETREE trial are no longer relevant for defining those who are at high risk of progression to severe disease. This is because most of the population in Canada has some natural or induced SARS-CoV-2 immunity and hospitalization rates among the general (and the high-risk population) have decreased over time. However, there are some patients, such as those who are severely immune suppressed and not able to produce a sufficient immune response (to either vaccination or infection), who are at high risk of progression and thus may benefit from antiviral treatments.</p>

Implementation issues	Response
<p>The Health Canada indication and sponsor's reimbursement request specify "nonhospitalized adults and pediatric patients (weighing \geq 40 kg)."</p> <p>How are pediatric patients < 12 years of age and/or weighing < 40 kg who are at high risk for progression to severe COVID-19 but who are not hospitalized managed?</p>	<p>The clinical expert suggested that the possibility of antiviral treatment for these patients (< 12 years of age and/or weighing < 40 kg) should be discussed on a case-by-case basis with specialists who have knowledge of infectious diseases and experience managing pediatric patients.</p> <p>CDEC noted that no evidence was submitted for patients who are younger than 12 years of age and/or weighing less than 40 kg, and this patient population is beyond the scope of this recommendation. CDEC also noted that there is limited evidence in the group of those aged 12 to 18 years and recommended not to reimburse remdesivir in patients who are younger than aged 18 years.</p>
<p>Should the reimbursement criteria for remdesivir include consideration of nirmatrelvir-ritonavir before remdesivir (where appropriate), given ease of availability and access?</p>	<p>The clinical expert agreed that nirmatrelvir-ritonavir should be considered before remdesivir and that because of its IV administration, remdesivir has a significant impact on health care resources to administer compared to oral nirmatrelvir-ritonavir.</p> <p>CDEC noted that nirmatrelvir-ritonavir should not be used in combination with remdesivir and that, ideally, patients eligible for nirmatrelvir-ritonavir would be likely to receive it because of challenges with the IV administration of remdesivir.</p>
<p>Is it possible to align the reimbursement criteria for remdesivir with those for nirmatrelvir-ritonavir, where appropriate?</p>	<p>The clinical expert and CDEC agreed that it would be reasonable to align the reimbursement criteria of the 2 drugs, where appropriate.</p>
Considerations for prescribing of therapy	
<p>For patients who are not hospitalized, the recommended total treatment duration for remdesivir is 3 days.</p> <p>However, NIH has suggested that longer and/or additional courses of remdesivir may be used in patients who are immunocompromised and have prolonged, symptomatic COVID-19 with evidence of ongoing viral replication.</p> <p>How often do patients require longer and/or additional courses of remdesivir in clinical practice?</p>	<p>The clinical expert indicated that most patients in an outpatient setting receive remdesivir for 3 days and it would be rare to require longer and/or additional courses of the drug as prophylaxis for hospitalization in clinical practice.</p> <p>CDEC noted that there is no evidence for a treatment duration for remdesivir of more than 3 days in patients who are not hospitalized.</p>
<p>Is there any evidence to support the combination use of antiviral therapies?</p>	<p>The clinical expert and CDEC agreed that there is a lack of evidence to support the combination use of antiviral therapies, including remdesivir.</p>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDEC = Canadian Drug Expert Committee; eGFR = estimated glomerular filtration rate; NIH = National Institutes of Health; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULN = upper limit of normal.

Clinical Evidence

Systematic Review

Description of Studies

One multicentre, phase III, double-blind, RCT (the PINETREE trial, N = 584) assessed whether remdesivir reduced COVID-19–related hospitalizations (defined as at least 24 hours of acute care) or all-cause death by

day 28 compared to placebo in patients weighing at least 40 kg who had confirmed SARS-CoV-2 infection, were not hospitalized, and were at high risk for progression to severe COVID-19 (risk based on prespecified patient characteristics at the time the study was conducted). Secondary and exploratory end points included COVID-19–related MAVs, all-cause mortality, new requirement for oxygen supplementation, ICU admissions, mechanical ventilation, and patient-reported symptom alleviation.

The mean age of patients was 50 (standard deviation = 15.1) years and demographic characteristics were generally balanced between the treatment groups. Patients younger than 60 years must have had at least 1 preexisting risk factor to participate. Across treatment groups, the most frequently reported baseline risk factors were diabetes (62%), obesity (56%), hypertension (48%), and chronic lung disease (24%), while other comorbidities were less common (less than 10% of patients had cardiovascular or cerebrovascular disease, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease). Individuals were excluded if they had any other antiviral treatment or vaccination against SARS-CoV-2.

Efficacy Results

COVID-19–Related Hospitalization or All–Cause Death

Two patients (0.7%) who received remdesivir and 15 patients (5.3%) who received placebo met the primary efficacy end point (HR = 0.13; 95% CI, 0.03 to 0.59; P = 0.0076) of COVID-19–related hospitalization (defined as at least 24 hours of acute care) or all-cause death by day 28. The number needed to treat was 22, as calculated by CADTH. A sensitivity analysis using baseline stratification factors as strata supported the results of the primary analysis. The primary composite outcome was driven by COVID-19–related hospitalizations as there were no deaths in either group by day 28. Furthermore, all COVID-19–related hospitalizations occurred by day 14 and the number of events by day 14 was the same as that by day 28.

Two subgroups were considered relevant to the CADTH review. Of the 15 patients who were residing in a skilled nursing facility and the 23 patients who had a baseline risk factor of being immunocompromised, none experienced a COVID-19–related hospitalization or death from any cause by day 28.

COVID-19–Related MAVs or All–Cause Death

By day 28, 4 patients (1.6%) in the remdesivir group and 21 patients (8.3%) in the placebo group met the composite end point of COVID-19–related MAVs (defined as medical visits attended in person by the patient and a health care professional) or all-cause death (HR = 0.19; 95% CI, 0.07 to 0.56). By day 14, 2 patients (0.8%) in the remdesivir group and 20 patients (7.9%) in the placebo group met the composite end point (HR = 0.10; 95% CI, 0.02 to 0.43).

Patients Progressing to Requiring Oxygen Supplementation

Of the 6 patients who progressed to requiring oxygen supplementation by day 28, 1 (0.4%) was in the remdesivir group and 5 (1.8%) were in the placebo group.

Patients Admitted to the ICU

Of the 6 patients who were admitted to the ICU by day 28, 3 (1.1%) were in the remdesivir group and 3 (1.1%) were in the placebo group.

Patients Started on Mechanical Ventilation

One patient (0.4%) in the trial (randomized to the placebo group) required mechanical ventilation by day 28.

COVID-19–Adapted FLU-PRO Plus

The FLU-PRO is a standardized questionnaire for reporting influenza symptoms in clinical trials that categorizes 32 items or symptoms into 6 domains (i.e., nose, throat, eyes, chest or respiratory, gastrointestinal, and body or systemic). The FLU-PRO Plus is adapted for assessing COVID-19 and includes a seventh domain for senses (2 items: loss of taste and smell). Patients rate the extent of their symptoms from 0 (not at all) to 4 (very much) for the past 24 hours. The mean score of symptoms for each domain is used to determine a total score.

Baseline data captured before the first dose were gathered for 66 patients in the remdesivir group and 60 patients in the placebo group. For this subset of patients, 23 patients in the remdesivir group and 15 patients in the placebo group reported alleviation (mild or absent) of baseline COVID-19 symptoms (HR = 1.41; 95% CI, 0.73 to 2.69) at day 14.

Harms Results

In the PINETREE trial, 42.3% of patients in the remdesivir group and 46.3% of patients in the placebo group reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs in the trial included nausea (10.8% for the remdesivir group and 7.4% for the placebo group), headache (5.7% for the remdesivir group and 6.0% for the placebo group), and cough (3.6% for the remdesivir group and 6.4% for the placebo group). In general, the incidences of harms were similar between the treatment groups.

Overall, 1.8% of patients in the remdesivir group and 6.7% of patients in the placebo group reported at least 1 serious AE. The most common serious AEs were related to COVID-19 and pneumonia.

In total, 0.7% of patients in the remdesivir group and 1.8% of patients in the placebo group stopped treatment due to a TEAE, which included COVID-19, pneumonia, respiratory failure, hypoxia, and dyspnea.

There were no patient deaths during the trial.

Elevated transaminases and hypersensitivity reactions were considered notable harms for the CADTH review. In the trial, 1 patient in the remdesivir group and 3 patients in the placebo group reported elevated alanine aminotransferase levels, while 1 patient in each of the treatment groups reported elevated aspartate aminotransferase levels. For hypersensitivity reactions, there were 6 patients in the remdesivir group and 4 patients in the placebo group who reported infusion site reactions. Anaphylactic reactions were not captured in the trial.

Critical Appraisal

The overall risk of bias in the PINETREE trial was low for the randomization process, deviations from intended interventions, missing outcomes data, and reported results. Study enrolment was stopped early and the final trial population was less than half (46.2%) of the planned sample size, though this did not have an impact on the statistical analysis of results as the primary efficacy end point was met. However, event rates were low during the trial, which limited the assessment of key clinical end points for this disease (e.g., requirements for supplemental oxygen, ICU admissions, and mechanical ventilation) and no deaths were reported. Efficacy, as observed, was driven by hospitalization only. It was not specified how the need for hospitalization or MAVs was determined and this may have been subjective. The trial also did not report what the causes for hospitalization or MAVs were, aside from being COVID-19–related, which itself was not further defined. No minimal important difference for the FLU-PRO Plus was identified from the literature and the clinical expert confirmed that it is not an instrument used in clinical practice. The trial was relatively short in duration and there is a lack of long-term safety evidence for remdesivir.

The intervention and treatment setting in the trial were considered generalizable to clinical practice in Canada. Considering when the trial took place (September 2020 to May 2021) and the significant changes in population immunity, viral pathogenesis, and disease management since then, the clinical expert consulted by CADTH indicated that the eligibility and baseline characteristics are no longer relevant to how remdesivir would be used in practice today. There were 8 adolescent patients in the trial and there is limited data to inform the use of remdesivir in patients aged 12 years or older. The trial excluded individuals who had received COVID-19 vaccinations, which greatly limits the generalizability of the results to current practice, and it is expected that the magnitude of the treatment effect would be smaller than that reported in the trial. The definition for high risk of progression to severe COVID-19 has narrowed over time to focus on vaccination status, severe immunocompromised status, and older age, and infection with current SARS-CoV-2 variants no longer carries a high risk of hospitalization. Relevant subgroup analyses were not available and/or not informative for these populations of interest. According to the expert, most of the comorbidities listed for enrolment eligibility alone are no longer considered to significantly increase the risk of worse disease outcomes. Evidence for the treatment effect of remdesivir was largely based on hospitalization (with no conclusions on the impact of remdesivir on death), which varies among different clinical practices and regions (no trial sites were in Canada), and the availability of health care resources. The PINETREE trial took place before the omicron variant was the predominant circulating strain; therefore, the estimate of treatment effect from the trial may not be applicable in the context of the current COVID-19 treatment landscape.

Long-Term Extension Studies

No long-term extension studies were submitted for this review.

Indirect Comparisons

No indirect treatment comparisons were submitted for this review.

Studies Addressing Gaps in the Evidence From the Systematic Review

Based on the information provided from the pivotal PINETREE trial, the sponsor identified an evidence gap for the effectiveness of remdesivir on patients with COVID-19 who are vaccinated, immunosuppressed, and at high risk for disease progression but are not hospitalized.

Description of Studies

From December 1, 2021, to April 30, 2022 (early in the period when omicron became the dominant circulating variant), a total of 196 patients in Mexico who were considered high risk were diagnosed with COVID-19; 126 of these patients were included in the prospective real-world evidence study (43% received remdesivir and 57% did not receive remdesivir). The baseline clinical characteristics were similar between the groups and autoimmune diseases (31%), solid organ transplant (25%), and malignant neoplasms (19%) were the most common immunocompromising conditions. Most patients were vaccinated (79%) and immunosuppressed (94%). The primary efficacy composite outcome was all-cause hospitalization or death at 28 days after symptom onset.

Efficacy Results

Treatment with remdesivir significantly reduced the likelihood of hospitalization or death (adjusted HR = 0.16; 95% CI, 0.06 to 0.44; $P < 0.01$). The results were largely driven by all-cause hospitalization events (5 and 22 patients in the remdesivir and control groups, respectively) compared to all-cause deaths (0 and 9 patients in the remdesivir and control groups, respectively). There were 20 COVID-19–related hospitalizations and all were from the control group. Diabetes mellitus was strongly associated with the primary outcome in both groups. Prior SARS-CoV-2 infection or vaccination were not independently associated with COVID-19 progression.

Harms Results

Harms results were not reported in the study.

Critical Appraisal

Overall, this was a small (54 remdesivir users and 72 nonusers) observational study that used data from a single tertiary referral centre for a highly selected group of patients with immunosuppression in Mexico City to examine the relationship between remdesivir exposure and 28-day hospitalization or mortality between December 2021 and April 2022. There were minimal details provided about data suitability (e.g., provenance, relevance, data quality).

The study was submitted to address gaps in the RCT evidence; however, it is at risk of bias and residual confounding, and has the potential for unmeasured confounders. Population disease exposure, as well as circulating variants, have changed substantively since the time of this study, limiting the generalizability of these findings to the current COVID-19 treatment landscape. Because of these limitations, the comparative effectiveness estimates may be biased, and it is not possible to quantify or identify the direction of the bias. The results were susceptible to bias because of potential imbalances in unmeasured confounders. Therefore, it is challenging to make any conclusions about the treatment effect of remdesivir on reduction in hospitalization or mortality at day 28 compared with non-remdesivir treatment for outpatients who are

immunosuppressed, vaccinated, and at high risk for COVID-19 progression in a health care setting in Mexico from this study.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Patients with COVID-19 at high risk for progression to severe disease who are not hospitalized
Treatment	Remdesivir
Dose regimen	200 mg on day 1, followed by 100 mg once daily for an additional 2 days (for a total treatment duration of 3 days)
Submitted price	Remdesivir 100 mg vial: \$660.53 per vial
Submitted treatment cost	\$2,642.12 per patient, based on a 3-day treatment duration
Comparator	SoC, comprising over-the-counter and off-label steroid medications
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	12 weeks
Key data sources	PINETREE trial ACTT-1 trial and real-world evidence (Mozaffari et al., 2023) to inform inpatient clinical efficacy
Key limitations	<ul style="list-style-type: none"> The population studied in the PINETREE trial does not accurately reflect the population at risk for progression to severe COVID-19 today. This is because of higher vaccination rates and the emergence of the Omicron strain of COVID-19, which was not present at the time of the PINETREE trial. 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 the PINETREE trial. The risk of hospitalization was informed by the PINETREE trial and does not accurately reflect the current risk of hospitalization for patients with COVID-19 in the current setting in Canada. The level of care patients require upon hospital admission was informed by the ACTT-1 trial and does not accurately reflect the illness severity status of patients upon hospital admission in the current setting in Canada. The hospitalization costs applied by the sponsor did not meet face validity and were estimated using data from an earlier COVID-19 wave that is not reflective of current health care resource use.
CADTH reanalysis results	<ul style="list-style-type: none"> To address some of the identified limitations, CADTH adjusted the risk of hospitalization, changed the baseline distribution for level of hospital care, and updated the COVID-19 hospitalization costs. In the CADTH reanalysis, the ICER for remdesivir was \$390,996 per QALY gained compared to SoC (incremental costs = \$2,372; incremental QALYs = 0.006). A price of \$486 per 3-day treatment course (a reduction of approximately 82%) would be required for remdesivir to be considered

Component	Description
	<p>cost-effective at a threshold of \$50,000 per QALY gained.</p> <ul style="list-style-type: none"> When considering the number needed to treat to avoid a severe case of COVID-19 (hospitalization or death), based on the PINETREE trial, 22 individuals at high risk would need to be treated. Based on the predicted hospitalization rates following CADTH's change to the risk of hospitalization in the model, 122 individuals at high risk would need to be treated. When comparing the drug acquisition costs of remdesivir for 22 and 122 individuals (approximately \$63,000 and \$351,000) with the cost of a general ward admission to treat COVID-19 (\$20,000), a price reduction of approximately 68% to 94% would be required to ensure minimal financial impact to the health care system.

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SoC = standard of care.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the eligible population size is highly uncertain and the uptake of remdesivir is uncertain. CADTH reanalyses revised the number of COVID-19 cases reported, adjusted the age distribution of COVID-19 cases, removed the number of COVID-19 cases not reported, assumed that all reported cases were tested for COVID-19, and adjusted the uptake of remdesivir. In the CADTH base case, the 3-year budget impact of reimbursing remdesivir for patients with COVID-19 (weighing at least 40 kg) who have positive results of direct SARS-CoV-2 viral testing and are not hospitalized but are at high risk for progression to severe COVID-19, including hospitalization and death, is estimated to cost \$3,489,179 (\$1,163,060 in each of year 1, year 2, and year 3). The estimated budget impact is highly sensitive to the eligible population size and the uptake of remdesivir.

CDEC Information

Members of the Committee

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

Meeting date: June 27, 2024

Regrets: Three expert committee members did not attend.

Conflicts of interest: None



ISSN: 2563-6596

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for noncommercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines*.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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