Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Remdesivir (Veklury)

Indication: For the treatment of coronavirus disease 2019 (COVID-19) in nonhospitalized adults and pediatric patients (weighing at least 40 kg) 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 and death.

Sponsor: Gilead Sciences Canada, Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: July 2024
Report Length: 15 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 remdesivir be reimbursed for the treatment of coronavirus disease 2019 (COVID-19) in nonhospitalized adult patients 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 and death, only if the conditions listed in **Error! Reference source not found.** 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 nonhospitalized patients 12 years or older (weighing at least 40 kg) with confirmed SARS-CoV-2 infection, 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 and 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 the omicron (B.1.1.529) was the main circulating variant of SARS-CoV-2, patients were unvaccinated, and patients were enrolled based on a definition of high-risk that no longer meets the current definition used in clinical practice today, as 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 are 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.

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, as well as treatments that do not present contraindications with their current medications and therapies. CDEC noted that remdesivir could potentially address some of these needs in nonhospitalized patients at high-risk for progression to severe COVID-19 such as those with moderate to severe immune suppression.

Using the sponsor-submitted price for remdesivir, the incremental cost-effectiveness ratio (ICER) as estimated by CADTH for remdesivir was $390,996 per quality-adjusted life-year (QALY) gained compared with standard of care to treat COVID-19 in nonhospitalized adults and pediatric patients who are at high-risk for progression to severe COVID-19. A price reduction would be required for remdesivir to achieve an ICER of $50,000 per QALY gained. There is uncertainty in the estimation of the price reduction due to the limitations in the clinical evidence base.

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 treatment of COVID-19 in adult patients	There is insufficient evidence that remdesivir is clinically superior or inferior to nirmatrelvir-ritonavir currently reimbursed for COVID-19. 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 due to its oral format and the practical administrative challenges with IV remdesivir.	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. CDEC also noted the challenges associated with accessing an infusion clinic for the IV administration and post-infusion 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. CDEC noted that for adult patients, public drug programs may consider reimbursing remdesivir in patients who cannot receive nirmatrelvir-ritonavir due to contraindications with their current medications.
Prescribing		
2. Duration of treatment with remdesivir should not exceed 3 days	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 non-hospitalized patients	
3. Not to be used in combination with any other antiviral medication for COVID-19, including nirmatrelvir-ritonavir.	There is no evidence to determine the effects of remdesivir when used in combination with other antiviral medications for COVID-19.	
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.	—

Reimbursement condition	Reason	Implementation guidance
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; PCR = polymerase chain reaction; RAT = rapid antigen tests.

Discussion Points

- CDEC discussed the unmet need for patients who cannot receive nirmatrelvir-ritonavir due to contraindications with their current medications. CDEC noted that remdesivir could potentially address that need in nonhospitalized patients at high-risk for progression to severe COVID-19 such as those with moderate to severe immune suppression.
- Given that remdesivir is administered by intravenous infusion for a duration of 3 days, CDEC discussed the implementation challenges associated with accessing an infusion clinic for the IV administration and post-infusion 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 the progression to severe COVID-19 have changed over time. Earlier in the pandemic, a wide range of risk factors were identified, which included older age, cardiovascular disease, diabetes mellitus, hypertension, cerebrovascular disease, dementia, neurodevelopmental disorders, and chronic kidney disease. CDEC also noted that at the time of issuing this recommendation, the relevance of these risk factors for progressing to severe disease has changed; as population immunity has increased over time and with the emergence of new variants, the proportion and characteristics of patients being hospitalized or dying due to COVID-19 have evolved.
- 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). Patients of greatest concern include 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.
- CDEC recognized that patients who are at increased risk for severe COVID-19 need access to treatments that are effective against COVID-19. Because individuals who have a higher risk for severe COVID-19 often live with an existing acute or chronic condition(s), these individuals need a variety of treatments that do not present contraindications with their current therapies. In addition, patients need treatments that are effective against different variants of COVID-19.
- CDEC noted that there is a difference between high or higher risk of hospitalization and death, and those who would actually benefit from remdesivir. In its deliberations, CDEC considered the evidence available and its relevance to the real-world disease context.
- 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 due to external validity limitations in the study. These included: the population enrolled in the PINETREE trial does not represent the population at risk for severe COVID-19 infection in 2024 due to changes in factors considered to put a patient at high-risk of severe COVID-19 infection, there are now different circulating strains with differing virulence, 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 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 non-hospitalized adolescent patients with COVID-19, as only 5 patients in the age group 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 non-hospitalized adolescent patients with COVID-19.

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. The 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 (not requiring 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 nonhospitalized adults and pediatric patients (weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization and death. For this CADTH review, the sponsor has requested reimbursement of remdesivir for the treatment of COVID-19 in nonhospitalized patients who are 12 years of age or older (weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization 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 nonhospitalized patients.

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 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 (RWE) 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 who 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 due to 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 Experts Consulted by CADTH

The clinical expert consulted by CADTH stated that the aim of treatment for nonhospitalized patients with SARS-CoV-2 infection 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 due to intolerance and drug-drug interactions. According to the clinical expert, the evidence supporting the claim that either drug reduces the 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 patients based on their underlying illness. The expert emphasized that specific viral testing is necessary to differentiate SARS-CoV-2 infection from other influenza-like illnesses and for access to treatment.

More recently, fewer patients are being admitted to the hospital for COVID-19 due to mild disease trajectory, and ICU admissions are rare. However, patients who are severely immune compromised (e.g., 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. As per the expert, commonly used clinical trial outcomes (e.g., hospitalization, ICU admissions, and death) are also important in practice. Remdesivir for nonhospitalized patients 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-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 nonhospitalized, symptomatic patients with solid organ transplants, 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., nursing and 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, 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, 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	
Eligibility criteria for the pivotal trial included the following: • Confirmed SARS-CoV-2 infection; • Age ≥ 18 years, or age ≥ 12 and < 18 years 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; and • Not requiring hospitalization (i.e., > 24 hours of acute care). Patients were excluded based on the following: • 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 m^2). Are the eligibility criteria from the pivotal trial appropriate as reimbursement criteria for this indication?	The clinical expert and CDEC agreed that due to 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 treatment of COVID-19 in adult patients. The clinical expert and CDEC agreed that it is essential that symptomatic patients 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. 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

Implementation issues	Response
How should “confirmed SARS-CoV-2 infection” be determined? 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)?	disease. This is due to the fact that most of the population in Canada has some natural or induced SARS-CoV-2 immunity and that 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.
The Health Canada indication and sponsor’s reimbursement request specify “nonhospitalized adults and pediatric patients (weighing ≥ 40 kg).” How are nonhospitalized pediatric patients < 12 years of age and/or weighing < 40 kg who are at high-risk for progression to severe COVID-19 managed?	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. 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 is limited evidence in the age group 12 to 18 years of age and recommended not to reimburse remdesivir in patients who are younger than 18 years of age.
Should reimbursement criteria for remdesivir include consideration of nirmatrelvir-ritonavir prior to remdesivir (where appropriate), given ease of availability and access?	The clinical expert agreed that nirmatrelvir-ritonavir should be considered before remdesivir and that due to its IV administration, remdesivir has a significant impact on health care resources to administer compared to oral nirmatrelvir-ritonavir. CDEC noted that nirmatrelvir-ritonavir should not be used in combination with remdesivir, CDEC also noted that ideally, patients eligible for nirmatrelvir-ritonavir would be likely to receive it due to challenges with IV administration of remdesivir
Is it possible to align the reimbursement criteria for remdesivir with that for nirmatrelvir-ritonavir, where appropriate?	The clinical expert and CDEC agreed that it would be reasonable to align reimbursement criteria of the 2 drugs, where appropriate.
Considerations for prescribing of therapy	
For nonhospitalized patients, the recommended total treatment duration for remdesivir is 3 days. However, NIH has suggested that longer and/or additional courses of remdesivir may be used in immunocompromised patients with prolonged, symptomatic COVID-19 with evidence of ongoing viral replication. How often do patients require longer and/or additional courses of remdesivir in clinical practice?	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. CDEC noted that there is no evidence for a treatment duration for remdesivir for more than 3 days in nonhospitalized patients

Implementation issues	Response
Is there any evidence to support combination use of antiviral therapies?	The clinical expert and CDEC agreed that there is a lack of evidence to support combination use of antiviral therapies, including remdesivir.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; 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 nonhospitalized patients weighing at least 40 kg with confirmed SARS-CoV-2 infection, and who 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 medically-attended visits (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 [SD] = 15.1) years and demographic characteristics were generally balanced between 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, and 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 (0.7%) patients who received remdesivir and 15 (5.3%) patients 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 (1.6%) patients in the remdesivir group and 21 (8.3%) patients 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 (0.8%) patients in the remdesivir group and 20 (7.9%) patients 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 (0.4%) patient in the trial (randomized to the placebo group) required mechanical ventilation by day 28.

COVID-19–adapted InFLUenza Patient-Reported Outcome (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 (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 prior to 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 remdesivir and 7.4% for placebo), headache (5.7% for remdesivir and 6.0% for placebo), and cough (3.6% for remdesivir and 6.4% for placebo). In general, the incidences of harms were similar between 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 adverse event (SAE). The most common SAEs 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 enrollment 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 since the primary efficacy end point was met. However, event rates were low during the trial limiting 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. The efficacy, as observed, was driven by hospitalization only. It was not specified how the need for hospitalization or MAVs was determined and 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 (MID) 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 12 years of age 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 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 enrollment 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, regions (no trial sites were in Canada), and 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 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 nonhospitalized, vaccinated, immunosuppressed patients with COVID-19 who are at high-risk for disease progression.

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 high-risk patients in Mexico were diagnosed with COVID-19, of whom 126 were included in the prospective RWE study (43% received remdesivir and 57% did not receive remdesivir). Baseline clinical characteristics were similar between groups; 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 non-users), 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 (provenance, relevance, data quality, etc.).

The study was submitted to address gaps in the RCT evidence; however, it is at risk of bias, residual confounding, and 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. Due to 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 due to 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

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Non-hospitalized patients with COVID-19 at high risk for progression to severe disease
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	• The population studied in the PINETREE trial does not accurately reflect the population at risk for progression to severe COVID-19 today. This is due to higher vaccination rates and the emergence of the Omicron strain of COVID-19, which was not present at the time of PINETREE. These differences represent a fundamental challenge in interpreting the results from the sponsor's submitted evidence dossier and accompanying pharmacoeconomic model which are based PINETREE. • 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 infections 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 healthcare resource use.
CADTH reanalysis results	• To address some of the identified limitations, CADTH adjusted the risk of hospitalization, changed the baseline distribution for level of hospital care, and updated COVID-19 hospitalization costs.

Component	Description
	• 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 (reduction of approximately 82%) would be required for remdesivir to be considered cost-effective at a threshold of $50,000 per QALY gained. • When considering the number needed to treat to avoid a severe case of COVID-19 (hospitalization or death), based on the PINETREE trial, 22 high risk individuals would need to be treated. Based on the predicted hospitalization rates following CADTH's change to the risk of hospitalization in the model, 122 high risk individuals 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, 3-year budget impact of reimbursing remdesivir for non-hospitalized COVID-19 patients (weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization 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 or remdesivir.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, 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:

3 expert committee members did not attend.

Conflicts of interest:

None