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CADTH Reimbursement Recommendation

Remdesivir (Veklury)

Indication: For the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen

Sponsor: Gilead Sciences Canada, Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Veklury?

CADTH recommends that Veklury should be reimbursed by public drug plans for the treatment of COVID-19 in hospitalized patients 12 years of age and older (weighing at least 40 kg) with pneumonia requiring supplemental oxygen if certain conditions are met.

Which Patients Are Eligible for Coverage?

Veklury should only be covered when initiated in hospitalized patients aged 12 years and older and weighing at least 40 kg with confirmed COVID-19 and requiring additional oxygen due to COVID-19 but not ventilation.
Veklury should not be covered when initiated in patients receiving artificial life support who cannot breathe on their own or in hospitalized patients who do not require oxygen support.

What Are the Conditions for Reimbursement?

Veklury should only be reimbursed if the treatment duration is 5 days and the cost is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 4 clinical trials suggested that remdesivir may prevent death in hospitalized patients aged 12 years and older with COVID-19 when disease severity requires oxygen support but does not require ventilation for life support. There is uncertainty regarding the generalizability of these results to current and future severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.
- Veklury may meet some needs that are important to patients, as it may prevent death in hospitalized patients with COVID-19 whose disease severity warrants oxygen support.
- 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. Therefore, a price reduction is required.
- Based on public list prices, Veklury is estimated to cost the public drug plans approximately $58 million over the next 3 years; however, this depends on the number of people hospitalized due to COVID-19.

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 most people with

Summary

COVID-19 experience mild symptoms, COVID-19 can lead to serious medical complications associated with high morbidity and mortality. The risk factors affecting the progression to severe disease have evolved over time. Population immunity has increased, and the number and characteristics of patients hospitalized due to COVID-19 have changed. According to the November 2023 WHO living guideline, patients at high risk of serious complications, including patients with compromised immune systems, have an estimated hospitalization rate of 6%.

Unmet Needs in COVID-19

Clinician input indicated there is a need for access to treatments that are effective across all disease severities and reduce administrative and health care resource burdens.

How Much Does Veklury Cost?

Treatment with Veklury is expected to cost approximately $3,963 per 5-day course.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that remdesivir be reimbursed for the treatment of COVID-19 in hospitalized patients aged 12 years and older (weighing at least 40 kg) with pneumonia requiring supplemental oxygen only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Findings from 4 randomized controlled trials (RCTs) (ACTT-1, WHO Solidarity, Spinner et al. [2020], and Wang et al. [2020]) conducted during the early phase of the COVID-19 pandemic in 2020 suggest that remdesivir may prevent death in hospitalized patients aged at least 12 years with COVID-19 whose disease severity warrants oxygen support but not ventilation. Treatment with remdesivir in the subgroup of patients receiving oxygen support may also be associated with decreased time to recovery or clinical improvement. In addition, remdesivir may be associated with a benefit in the incidence of new ventilation support for patients who were not ventilated at baseline. However, the effect on the duration of hospitalization is uncertain due to inconsistencies between the trials and small effect sizes. Remdesivir was well-tolerated in all included studies. Significant uncertainty exists regarding the generalizability of these results to current and future severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

The clinical expert consulted by CADTH noted that an ideal intervention for COVID-19 focuses on prevention, not treatment. For patients who do require treatment, a treatment option that is effective across all disease severities would be ideal. CDEC noted that remdesivir may prevent death in hospitalized patients whose disease severity warrants oxygen support.

Using the sponsor-submitted price for remdesivir, the incremental cost-effectiveness ratio (ICER) as estimated by CADTH for remdesivir was $3,748,693 per quality-adjusted life-year (QALY) gained compared with standard of care (SOC) to treat COVID-19 in hospitalized patients aged 12 years and older (weighing at least 40 kg) with pneumonia requiring supplemental oxygen. This was based on a reanalysis in which the overall mortality risk was adjusted by vaccine effectiveness against severe outcomes for individuals with the Omicron variant and in which the mortality benefit for remdesivir was applied only to patients receiving low-flow oxygen support. 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. Treatment with remdesivir should be reimbursed when initiated in hospitalized patients who are at least 12 years of age	Patients enrolled in 3 RCTs (ACTT-1, WHO Solidarity, and Wang et al. [2020]) were at least 18 years of age, while patients enrolled in 1 RCT (Spinner et al. [2020]) were at least 12 years of age	The reason for requiring supplemental oxygen should be directly attributable to the

Reimbursement condition	Reason	Implementation guidance
and weigh at least 40 kg with confirmed COVID-19 and require supplemental oxygen due to COVID-19 but do not require ventilation.	and weighed at least 40 kg. Subgroup analyses in ACTT-1 and WHO Solidarity demonstrated that remdesivir was associated with clinical benefit, including reduced mortality, specifically for the subgroup of patients who were receiving supplemental oxygen at baseline.	symptoms of COVID-19 infection and not due to comorbid conditions.
2. Treatment with remdesivir must not be reimbursed when initiated in patients who meet any of the following criteria: 2.1. are receiving mechanical ventilation 2.2. are receiving extracorporeal membrane oxygenation 2.3. are on room air do not require oxygen support.	Results of subgroup analyses by level of oxygen support required in ACTT-1 and WHO Solidarity did not demonstrate a significant benefit of remdesivir treatment in subpopulations of patients who either did not require any oxygen support or who had already progressed to ventilation or extracorporeal membrane oxygenation. In ACTT-1 and WHO Solidarity, benefits associated with remdesivir were demonstrated only in the subgroup of patients requiring oxygen support (low flow in ACTT-1 and low or high flow in WHO Solidarity).	—
Prescribing		
3. The duration of treatment with remdesivir is 5 days.	Although regimens of remdesivir of both 5 and 10 days are approved by Health Canada, there is no evidence to suggest a 10-day course of treatment with remdesivir improves outcomes relative to a 5-day course.	May be used in conjunction with standard of care, including steroids and therapeutic anticoagulation. Remdesivir is given for the entire course of treatment. Discontinuation is only necessary in the case of intolerable side effects.
Pricing		
4. A reduction in price.	The cost-effectiveness of remdesivir is highly uncertain. The ICER for remdesivir is $3,748,693 per QALY gained compared to standard of care alone in a reanalysis in which the overall mortality risk was adjusted by vaccine effectiveness against severe outcomes for the Omicron variant and the mortality benefit for remdesivir was applied only to patients receiving low-flow oxygen support. A price reduction of 92% 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.	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RCT = randomized controlled trial.

Discussion Points

- Currently, the WHO living guidelines and the Canadian treatment practice guidelines related to the management of COVID-19 recommend the use of remdesivir in patients with disease that is severe enough to require supplemental oxygen or organ support due to COVID-19, but not those who have already progressed to ventilation before the initiation of remdesivir. The clinical expert consulted agreed with this recommendation but noted to CDEC that this could change in the future as the virus evolves. Because remdesivir is already being used in clinical practice (especially earlier on in the pandemic), there are no expected changes to the current treatment paradigm based on this recommendation.
- There is substantial uncertainty due to lack of a direct body of evidence because of the rapidly changing nature of COVID-19. All the included RCTs were conducted in 2020 at the beginning of the COVID-19 pandemic. There are considerable differences between the prevalent variants of SARS-CoV-2 in 2020 versus present day. Moreover, there was not widespread access to COVID-19 vaccinations at that time, and population immunity and risk factors for progression to severe disease all differ now. CDEC discussed that the severity of COVID-19 and the likelihood of hospitalization or death directly related to COVID-19 are substantially lower in present day than earlier in the pandemic. However, the risks are not absent, and the rapidly changing nature of the virus and uncertainties about the future must be considered.
- Remdesivir does not necessarily meet all unmet needs associated with COVID-19 treatment; for example, there is an absence of targeted COVID-19 therapy that is beneficial for patients with all disease severities and an option with lower administration burden and health care resource burden would be ideal. However, in the absence of this hypothetical ideal therapy, CDEC discussed that it may be important to have access to remdesivir for the circumstance in which a patient may need it and potentially in the future if the risks associated with COVID-19 outbreaks increase again.
- Based on the Health Canada–recommended dosage, the duration of treatment with remdesivir in hospitalized patients older than 12 years of age weighing at least 40 kg is a minimum of 5 days up to a maximum of 10 days. Although most evidence evaluated 10-day regimens, 1 RCT compared both 5-day and 10-day regimens to a control group, and the longer regimen showed no additional benefit or harm. CDEC discussed that, in the absence of evidence in favour of 10-day treatment regimen, reimbursement should be for the 5-day regimen.
- CDEC discussed that results from the clinical evidence appeared to be largely driven by the subgroup of patients receiving low-flow oxygen support. Studies that reported subgroup effects were inconsistent regarding where high-flow oxygen was categorized in the studies, so there is uncertainty regarding whether patients receiving high-flow oxygen support benefited similarly to patients receiving low-flow oxygen support. The largest included study, WHO Solidarity, grouped patients receiving high-flow and low-flow oxygen together in 1 subgroup. As a result, CDEC concluded that extending reimbursement to patients on high-flow oxygen was prudent.

- CDEC also evaluated evidence from several real-world observational studies that were submitted to address gaps in the evidence provided in the pivotal studies, including efficacy and/or safety of remdesivir in patients who are immunocompromised, patients discharged after hospitalization for COVID-19, patients with post–COVID-19 condition (patients infected with the virus that causes COVID-19 who experience long-term effects from their infection beyond the acute infection), patients with renal disease, hospitalized patients also receiving dexamethasone, and patients who were vaccinated and not hospitalized as well as across different SARS-CoV-2 variants of interest (pre-Delta, Delta, and Omicron). There were substantial limitations in the reporting and generalizability of the real-world studies that precluded drawing strong conclusions from these studies.
- CDEC discussed the economic evidence and noted that the assumed mortality benefit for remdesivir is a key parameter influencing the results of the cost-effectiveness analysis. CDEC considered 4 reanalyses conducted by CADTH that used different assumptions for the mortality benefit for remdesivir. Based on the clinical evidence, which indicated the mortality benefit was largely driven by the subgroup of patients receiving low-flow oxygen support, CDEC determined that the reanalysis that applied a mortality benefit only to those patients with low-flow oxygen support, and reduced the overall COVID-19 mortality risk to better reflect the current COVID-19 context was the most appropriate reanalysis to consider. As such, CDEC considered the ICER and price reduction (i.e., 92%) derived from that analysis.

Background

COVID-19 is an illness caused by SARS-CoV-2. The rapid global spread of the virus led to a pandemic, as declared by WHO on March 11, 2020. Subsequently, the proliferation of COVID-19 has presented significant challenges to health care systems globally, including those in Canada. As of April 3, 2024, the cumulative number of reported COVID-19 cases and deaths in Canada were 4,946,090 and 59,034, respectively, and the weekly percentage of positive cases out of the total tests conducted was 5.2%. According to the Canadian Institute for Health Information, there were 120,524 hospitalizations due to COVID-19 in Canada from April 2022 to March 2023, compared to 125,986 hospitalizations due to COVID-19 in the previous year. In 2022–2023 , 10% of people admitted to hospital died in the facility and 13% were admitted to the intensive care unit (ICU). For those patients admitted to the ICU, 39% received ventilation. The estimated total cost of COVID-19 hospitalizations in 2022–2023 was approximately $2.9 billion, and costs continue to increase each fiscal year.

Patients with symptomatic COVID-19 have a wide range of symptoms from none or mild symptoms in most cases (e.g., fever, cough, headache, malaise, muscle pain, nausea, vomiting, loss of taste and smell) to severe symptoms, including pneumonia and acute respiratory distress syndrome. Severe cases are also associated with pulmonary embolism, arrhythmia, cardiovascular shock, and heart damage or heart attack. At its worst, COVID-19 can lead to critical illness; individuals can experience respiratory failure, septic shock, and/or various organ dysfunctions known to be associated with high morbidity and mortality. Mortality risk estimates reported by WHO for patients with nonsevere disease are 0.6% for those who are at high risk of

hospitalization, 0.3% for those who are at moderate risk of hospitalization, and 0.05% for those who are at low risk of hospitalization.

Remdesivir has been approved by Health Canada for the treatment of patients with COVID-19 who are at least 4 weeks of age and weigh at least 3 kg, have pneumonia, and need extra oxygen to help them breathe, as well as nonhospitalized adults and children weighing at least 40 kg with positive SARS-CoV-2 test results who are at high risk for progression to severe COVID-19, including hospitalization and death. For this review, the sponsor requested reimbursement of remdesivir for the treatment of COVID-19 in hospitalized patients aged 12 years or older (weighing at least 40 kg) with pneumonia requiring supplemental oxygen.

Remdesivir is an antiviral medication. It is available as a powder for solution for administration by IV infusion. The dosage recommended in the product monograph is 200 mg infusion on day 1 followed by 100 mg infusion daily in adults; in children it is 5 mg per kg of body weight on day 1 followed by 2.5 mg per kg of body weight daily. The duration of treatment with remdesivir is daily for at least 5 days up to a total of 10 days in hospitalized patients weighing at least 40 kg, daily for up to 10 days in hospitalized children (at least 4 weeks old and weighing at least 3 kg but less than 40 kg), and daily for 3 days starting within 7 days of the onset of symptoms in patients weighing at least 40 kg who are not hospitalized and are at increased risk of progressing to severe COVID-19.

Sources of Information Used by the Committee

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

- a review of 4 RCTs and 1 single-arm study in patients with COVID-19 and 9 real-world observational studies
- input from public drug programs that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with COVID-19
- input from 1 clinician group, the Ontario Health Infectious Diseases Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

No patient groups provided input for this review.

Input From Clinical Expert Consulted by CADTH

The clinical expert described that COVID-19 is no longer a significant cause of hospitalization and death because of the evolution of the virus since the beginning of the pandemic. The expert noted that an ideal intervention for COVID-19 focuses on prevention, not treatment. For patients who do require treatment, a

treatment option that is effective across all disease severities would be ideal as would oral delivery of the medication. A significant treatment goal is to reduce unnecessary antimicrobial use in COVID-19. However, there is an information gap regarding clinical data that is relevant to the currently prevalent variants because the majority of evidence was generated with early variants and may not apply to current variants.

The clinical expert noted that remdesivir may have a rare application given the lower prevalence of hospitalization and death caused by current SARS-CoV-2 variants. Remdesivir would be used in combination with other treatments as a first-line drug based on the WHO living guidelines for clinical management of COVID-19. It was also noted that remdesivir is unique in its antiviral action because it does not target host immune response like other therapies for COVID-19. The clinical expert stated that remdesivir would not change clinical practice because it is rarely used since the early stages of the pandemic.

For inpatients, those who are most in need of an intervention are those at risk of death. Diagnosis of COVID-19 is based on polymerase chain reaction (more accurate, more expensive, less accessible) or antigen (less accurate, less expensive, more accessible) testing. There is a lack of current data to support which patients would most benefit from remdesivir because the available data primarily evaluate early pandemic SARS-CoV-2 variants and patient populations that were mostly unvaccinated. However, the expert described that patients who are sick enough to require oxygen support as a result of COVID-19, but who have not yet progressed to needing ventilation, may be the most likely to benefit from remdesivir. This is reflected in trial data, but again, these trials were conducted in populations with different variants so there are serious limitations regarding the generalizability of the results. The expert speculated that the reason for this observation may be related to the pathogenesis of COVID-19 (i.e., earlier stages of disease are virologically mediated while later stages of disease are immune-mediated); therefore, the application of an antiviral such as remdesivir would be less helpful in patients whose medical distress is caused by immune response rather than virological activity. The clinical expert identified that the key outcomes (for patients already admitted to hospital) are initiation of oxygen or organ support and rate of mortality. Meaningful response would be a change in status of oxygen or organ support requirements, which does not vary by physician interpretation because they are objective outcomes. Clinical symptoms and viral load are not relevant clinical outcomes and do not correlate with the objective outcomes. The clinical expert stated that remdesivir would generally be given for the entire treatment course (5 days or 10 days), and it would not be stopped due to progression or additional treatments, although it may be stopped as a result of adverse events (AEs) if necessary. Dosing is 200 mg on the first day followed by 100 mg daily. The expert noted that the shortest effective duration of treatment should be used. Treatment with remdesivir would be prescribed for inpatients in hospital settings, with no need for a specialist to diagnose or treat.

Clinician Group Input

One clinician group, the Ontario Health Infectious Diseases Advisory Committee (consisting of input from 4 clinicians), responded to CADTH's call for clinician group input. Information was gathered through discussion.

According to the clinician group, the treatment regimen for COVID-19 for hospitalized patients includes supplemental oxygen therapy and immunomodulators, such as corticosteroids (recommended as first-

line treatment for hospitalized adults with COVID-19 requiring any supplemental oxygen), Janus kinase inhibitors, and anti-interleukin (IL)–6 receptor monoclonal antibodies. Remdesivir can be added to other immunomodulatory agents that work on the hyperinflammatory pathway that drives the disease course in the later stages of illness.

The main treatment goals are to accelerate recovery; reduce the severity of symptoms and duration of hospitalization; prevent progression to critical COVID-19 disease conditions and long-term sequelae; prevent the need for new high-flow supplemental oxygen, noninvasive ventilation (e.g., bilevel positive airway pressure [BiPAP]), mechanical ventilation, or extracorporeal membrane oxygenation (ECMO); and prevent death.

The clinician group indicated that not all patients respond to currently available treatment. They also indicated there are limitations with remdesivir, such as the drug formulation (IV) and the lack of RCTs on the effectiveness of remdesivir on all variants, especially Omicron.

According to the clinician group, hospitalized patients best suited for treatment with remdesivir are those who require supplemental low-flow oxygen. Remdesivir should ideally be started early in the disease course when viral replication predominates.

The input stated that outcomes used in clinical practice typically align with those used in clinical trials and would be considered clinically meaningful responses (e.g., duration of hospitalization, ICU admission, ICU length of stay, time to improvement in clinical status, progression to high-flow oxygen or noninvasive ventilation, progression to mechanical ventilation or ECMO, time to receipt of mechanical ventilation, time to clinical improvement, mortality, length of hospital stay, serious AEs (SAEs), and withdrawals from study due to AE).

According to the clinician group, the factors that should be considered when deciding to discontinue treatment with remdesivir include disease progression to critical COVID-19, severe allergic reaction, adverse drug reaction, and AEs.

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 affect the implementation of a CADTH recommendation for remdesivir:

- relevant comparators
- considerations for initiation of therapy
- considerations for the prescribing of therapy
- system and economic issues.

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
Relevant comparators	
To date, COVID-19 therapeutics have been procured, paid for, and distributed to provinces and territories by the federal government. The criteria used to determine coverage may be significantly different across provinces and territories.	This is a comment from the drug programs to inform CDEC deliberations. The clinical expert confirmed there are significant differences between jurisdictions in Canada.
Considerations for initiation of therapy	
Submitted trials used different inclusion criteria and definitions of severe disease. If recommended for funding, it will be important to clearly define any disease score or stage (e.g., specific severity or maximum duration of symptoms) required for eligibility. What patients benefit the most from treatment with remdesivir? What patients may not have appreciable benefit? For example, consider: • need for supplemental oxygen • use of high-flow nasal cannula oxygen • use of noninvasive or invasive ventilation, extracorporeal membrane oxygenation.	The clinical expert noted to CDEC that the COVID-19 virus changes quickly and clinical practice in Canada follows the WHO living guidelines for treatment of COVID-19. The clinical expert added that, based on data from the early pandemic, it appears patients receiving supplemental low-flow oxygen benefit from treatment with remdesivir and patients receiving high-flow oxygen may also benefit (less certain due to conflicting data). In contrast, patients who are not sick enough to need oxygen or organ support and patients who have already progressed to ventilation do not appear to benefit from treatment with remdesivir based on current data and the WHO guidelines as described by the clinical expert. Currently, these patients with a "medium prognosis" are those who may need access to remdesivir, according to the clinical expert. However, the clinical expert noted that this could change in the future as the virus evolves. CDEC recommended that remdesivir be reimbursed only for patients with COVID-19 who are receiving supplemental low-flow or high-flow oxygen.
Considerations for prescribing of therapy	
Should remdesivir be given in a duration of 5 or 10 days? Does the ideal duration vary by patient? Does dosing vary?	The clinical expert described that duration of treatment can be 5 or 10 days and there are no firm guidelines on which to use. The dosage of remdesivir does not otherwise vary (200 mg on the first day followed by 100 mg daily). Because the data do not show a clear benefit or harm at 10 days over 5 days, the clinical expert suggested that the lowest effective duration should be used. However, because most trials used 10-day regimens, there is a lack of data to support a decision between them. CDEC recommended that the maximum duration of treatment with remdesivir should be 5 days.
System and economic issues	
The indication under consideration is for hospital inpatients. Funding for drugs administered to hospital inpatients generally comes from hospital global budgets and is not provided by public drug programs.	This is a comment from the drug programs to inform CDEC deliberations.

CDEC = Canadian Drug Expert Committee.

Clinical Evidence

Description of Studies

The primary sources of evidence for review included 5 studies, 3 of which were RCTs conducted in adults (ACTT-1, WHO Solidarity, and Wang et al. [2020]), 1 was an RCT conducted in patients aged at least 12 years (Spinner et al. [2020]), and 1 was a single-arm, open-label study in pediatric patients (CARAVAN). The studies were all conducted in patients hospitalized with COVID-19 requiring inpatient treatment. ACTT-1 (N = 1,062) was a double-blind, placebo-controlled, multicentre, international, phase III RCT in adults aged at least 18 years admitted to hospital with confirmed COVID-19. The study by Wang et al. (2020) (N = 237) was a double-blind, placebo-controlled, multicentre RCT conducted in 10 hospitals in China in adult patients aged at least 18 years admitted to hospital with confirmed COVID-19. WHO Solidarity (N = 8,320 in the remdesivir and control groups) was an open-label, SOC-controlled, international RCT of several putative treatments for COVID-19 in adults with definite COVID-19, although only the remdesivir group and its associated control group are described for the purpose of this report. The study by Spinner et al. (2020) (N = 596) was an open-label multicentre international RCT that evaluated 5 or 10 days of remdesivir against SOC in hospitalized patients aged at least 12 years with moderate COVID-19 pneumonia. Finally, CARAVAN (N = 53) was a single-arm, open-label, phase II/III, international study in pediatric patients; however, only those in cohort 1 (N = 12) were at least 12 years of age and weighed at least 40 kg. The outcomes of interest for this review were mortality, duration of hospitalization, time to clinical recovery or improvement, and initiation of ventilation.

Efficacy Results

Mortality

In the ACTT-1 study's intention-to-treat (ITT) population, the risk of death by day 15 was lower in the group treated with remdesivir for 10 days compared with the placebo group (hazard ratio [HR] = 0.55; 95% confidence interval [CI], 0.36 to 0.83; P = 0.004). At day 29, the difference between groups was less apparent (HR = 0.73; 95% CI, 0.52 to 1.02; P = 0.066). The median time to death through day 15 or day 29 was not estimable for either treatment group in the ITT or as-treated populations. In ad hoc subgroup analyses of mortality by actual disease stratum or ordinal score, as defined by level of oxygen support required, the greatest differences in the percentage of deaths for participants with known mortality status at day 29 in the group treated with remdesivir for 10 days compared with the placebo group was observed in the subgroup with a baseline ordinal score of 5 (i.e., patients receiving low-flow oxygen), with a mortality rate of 4.1% in the group treated with remdesivir for 10 days (9 of 222 participants) compared to 12.8% in the placebo group (25 of 195 participants) (HR = 0.30; 95% CI, 0.14 to 0.64; P < 0.001, without adjustments for multiplicity). In the actual severe disease stratum, the mortality rate was 12.5% in the remdesivir group (57 of 457 participants) versus 16.3% in the placebo group (74 of 453 participants). Patients with a baseline ordinal score of 5 also represented the most populous subgroup by ordinal score in the ACTT-1 study.

In the study by Wang et al. (2020), mortality was similar between the treatment groups at day 28 in the ITT population. In the remdesivir group, 22 of 158 (14%) patients died and 10 of 78 (13%) patients in the placebo group died, yielding a difference of 1.1% (95% CI, −8.1% to 10.3%; P not reported). Mortality was similar

between treatment groups in subgroup analyses of patients who used remdesivir "early" (within 10 days of symptom onset) or "late" (more than 10 days after symptom onset). However, the numerical results differed in direction: mortality was numerically higher in the placebo group in the early use subgroup, whereas mortality was numerically higher in the remdesivir group in the late use subgroup.

In the WHO Solidarity study, of 8,275 patients included in the overall remdesivir analyses, 602 of 4,146 (14.5%) assigned to the remdesivir group and 643 of 4,129 (15.6%) assigned to the control group died (risk ratio [RR] = 0.91; 95% CI, 0.82 to 1.02; P = 0.12). These analyses of in-hospital mortality included 15 palliative discharges in the remdesivir group and 11 in the control group. Analyses were also subdivided by oxygen support requirements at baseline; of these, the subgroup of patients who were already on oxygen (low or high flow) but not ventilated at baseline demonstrated a benefit of remdesivir over control in terms of in-hospital mortality (RR = 0.87; 95% CI, 0.76 to 0.99; P = 0.03).

In the study by Spinner et al. (2020), in the group treated with remdesivir for 10 days (n = 193), the group treated with remdesivir for 5 days (n = 191), and the SOC group (n = 200), a total of 3 (2%), 2 (1%), and 4 (2%) patients, respectively, died from any cause through 28 days of the trial. The Kaplan-Meier estimates of all-cause mortality at day 28 were 1% (95% CI, 0.0% to 2.6%; P = 0.43 versus SOC) for the group treated with remdesivir for 5 days, 2% (95% CI, 0.0% to 3.6%; P = 0.72 versus SOC) for the group treated with remdesivir for 10 days, and 2% (95% CI, 0.1% to 4.1%) for the SOC group.

In cohort 1 (n = 12) of the CARAVAN study, there was 1 treatment-emergent death (8.3%).

Duration of Hospitalization

Only the ACTT-1 study results showed a benefit of remdesivir on the duration of hospitalization. The median days of initial hospitalization, including imputations for participants who died, was 12 days (interquartile range [IQR], 6 to 28 days) in the remdesivir group (n = 541) and 17 days (IQR, 8 to 28 days) in the placebo group (n = 521), yielding a median difference of 5 days shorter with remdesivir (95% CI, 2.3 to 7.7 days).

In contrast, the WHO Solidarity study found that allocation to remdesivir delayed discharge by approximately 1 day during the 10-day treatment period owing to the duration of the treatment regimen itself potentially delaying discharge.

Both Wang et al. (2020) and Spinner et al. (2020) reported that there was no difference observed between treatment arms on the duration of hospitalization.

In cohort 1 of the CARAVAN study, the mean duration of hospitalization from day 1 (days from first dose to date discharged alive: n = 9) was 12 days (standard deviation [SD] = 5.5 days) and the median was 12 days (IQR, 8 to 15 days; range, 6 to 24 days).

Time to Recovery or Clinical Improvement

Results from ACTT-1 were stratified by disease severity within the ITT population; "mild-moderate" disease was defined as having a blood oxygen saturation of more than 94% and a respiratory rate of fewer than 24 breaths per minute without supplemental oxygen and "severe" disease was defined as requiring mechanical ventilation, requiring oxygen, blood oxygen saturation equal to or less than 94% on room air, or

tachypnea (respiratory rate ≥ 24 breaths per minute). In patients in the mild to moderate disease stratum at randomization (remdesivir: n = 82; placebo: n = 77), the median time to recovery was 5 days (95% CI, 4 to 6 days) in the remdesivir group and 7 days (95% CI, 5 to 9 days) in the placebo group (risk of recovery ratio = 1.10; 95% CI, 0.80 to 1.53). In patients in the severe disease stratum at randomization, the median time to recovery was 12 days (95% CI, 10 to 14 days) in the remdesivir group versus 19 days (95% CI, 16 to 21 days) in the placebo group (risk of recovery ratio = 1.34; 95% CI, 1.14 to 1.58). In patients with any disease severity, the median time to recovery in the ITT population was 10 days (95% CI, 9 to 11 days) in the remdesivir group (n = 541) and 15 days (95% CI, 13 to 18 days) in the placebo group (n = 521). Subgroup analyses were also conducted according to ordinal score at baseline (defined by the level of oxygen support required). Only patients who required supplemental oxygen (but not high-flow oxygen or any level of ventilation; i.e., ordinal score level 5) demonstrated a benefit of remdesivir in time to recovery; this was also the most populous subgroup (remdesivir: n = 232; placebo: n = 203).

In the ITT population in the study by Wang et al. (2020), the time to clinical improvement in the remdesivir group (median = 21.0 days; IQR = 13.0 to 28.0 days) was not significantly different from that of the control group (median = 23.0 days; IQR, 15.0 to 28.0 days; HR = 1.23; 95% CI, 0.87 to 1.75).

In the study by Spinner et al. (2020), there were no significant differences between the group treated with remdesivir for 10 days and the SOC group for the time to 2 points or greater improvement in clinical status (HR = 1.16; 95% CI, 0.93 to 1.43), time to 1 point or greater improvement in clinical status (HR = 1.10; 95% CI, 0.90 to 1.36), time to recovery (HR = 1.11; 95% CI, 0.90 to 1.37), or time to modified recovery (HR = 1.10; 95% CI, 0.90 to 1.36). Comparing the group treated with remdesivir for 5 days to the SOC group, there were also no significant differences between the groups for the time to 2 points or greater improvement in clinical status (HR = 1.15; 95% CI, 0.93 to 1.42), time to 1 point or greater improvement in clinical status (HR = 1.19; 95% CI, 0.97 to 1.47), time to recovery (HR = 1.18; 95% CI, 0.96 to 1.45), or time to modified recovery (HR = 1.19; 95% CI, 0.19 to 1.46).

The median time to recovery in cohort 1 of the CARAVAN study was 12 days (IQR, 6 to 24 days).

This outcome was not assessed in the WHO Solidarity study.

Initiation of Ventilation

This outcome was only assessed in the ACTT-1 and WHO Solidarity studies.

In the ACTT-1 study, the incidence rate of new noninvasive ventilation or high-flow oxygen use in patients who were not already on these supports (nor ventilated) at baseline was 0.17 (95% CI, 0.13 to 0.22) in the remdesivir group and 0.24 (95% CI, 0.19 to 0.30) in the placebo group. The incidence rate in the remdesivir group was numerically lower, but the 95% CIs of each group overlapped. The incidence rate of new invasive mechanical ventilation or ECMO use for patients not already on these supports at baseline was 0.13 (95% CI, 0.10 to 0.17) in the remdesivir group and 0.23 (95% CI, 0.19 to 0.27) in the placebo group. The incidence rate in the remdesivir group was numerically lower, but the 95% CIs of each group did not overlap.

In the WHO Solidarity study, patients in the remdesivir group had a lower rate of progression to ventilation (event RR = 0.88; 95% CI, 0.77 to 1.00; P = 0.04) and with a lower composite outcome of death or ventilation

(event RR = 0.84; 95% CI, 0.75 to 0.93; P = 0.001) when compared to the control group . For both outcomes, results for the subgroup of patients who were not on oxygen support at entry had an associated 95% CI that crossed null, whereas results for the subgroup of patients who were receiving low- or high-flow oxygen at entry showed a statistically significant benefit for both outcomes in favor of remdesivir group when compared to the control group. The latter subgroup was also much larger, so this subgroup (patients already on low- or high-flow oxygen at baseline) appears to drive the observed benefit of remdesivir for this outcome. In the Canadian substudy, CATCO, for patients who were not mechanically ventilated at baseline, 8.0% of those assigned to the remdesivir group required mechanical ventilation during the study compared to 15.0% of those assigned to the SOC group (RR = 0.53; 95% CI, 0.38 to 0.75).

Although duration of oxygen support use or ventilation was not selected as a key outcome of interest based on consultation with the clinical expert, related outcomes are summarized here. Briefly, median days on oxygen, noninvasive ventilation or high-flow oxygen, or invasive mechanical ventilation or ECMO were reported in the ACTT-1 study. Although statistical comparisons were not conducted and the IQRs overlapped between groups, the median days on oxygen or invasive mechanical ventilation or ECMO were lower in the remdesivir group compared to the placebo group. The median days were the same between groups for the median days on noninvasive ventilation or high-flow oxygen. The CATCO study reported that patients in the remdesivir group had significantly higher mean oxygen- and ventilator-free days at day 28. Wang et al. (2020) reported lower median days of invasive mechanical ventilation and lower median days of oxygen support in the remdesivir group compared to the placebo group, although the IQRs overlapped. Spinner et al. (2020) reported no significant difference between the remdesivir group and the SOC group for the duration of oxygen support. Therefore, there is some evidence to suggest there may be a modest benefit of remdesivir on duration of some forms of oxygen support, but the magnitude is uncertain and there is inconsistency between the studies.

Harms Results

Remdesivir was generally well-tolerated in all the included studies. The proportion of patients who experienced at least 1 AE ranged from 51% to 64% across the 4 RCTs and was 91.7% in cohort 1 of the CARAVAN study. The studies varied significantly in the specific AEs reported, but there was a trend across the trials of a focus on biomarkers related to kidney and liver function, hyperglycemia, and some clinical AEs (e.g., headache, constipation, pyrexia, and diarrhea, among others). If reported, AEs were generally similar between treatment groups, although in some cases there were numerically more AEs in the placebo or SOC group than the remdesivir group.

In the 4 RCTs, the proportion of patients who experienced at least 1 SAE ranged from 5% in both remdesivir groups of Spinner et al. (2010) study to 32% in the placebo group of the ACTT-1 study. In cohort 1 of the CARAVAN study, 5 (41.7%) patients experienced an SAE.

In ACTT-1, a higher proportion of patients experienced SAEs in the placebo arm (32%) than the remdesivir arm (25%). This was also the case in the Wang et al. (2020) study (26% in the placebo arm versus 18% in the remdesivir arm). In the Spinner et al. (2020) study, 5% of patients experienced at least 1 SAE in both

remdesivir groups (10 day and 5 day), whereas 9% of patients in the SOC group experienced at least 1 SAE. This outcome was not reported in the WHO Solidarity study.

The studies were inconsistent regarding which SAEs were reported. The most common AE reported in the ACTT-1 and Wang et al. (2020) studies was respiratory failure, which occurred in 7% and 10% of patients in the remdesivir groups, respectively, and in 11% and 8% of patients in the placebo groups, respectively.

Withdrawals due to AEs were relatively high in the ACTT-1 study, occurring in 11.1% of patients in the remdesivir group and 15% of patients in the placebo group. In the Wang et al. study, 15% and 13% of patients withdrew due to AEs in the remdesivir and placebo groups, respectively. In the WHO Solidarity study, 14.5% and 15.6% withdrew due to AEs in the remdesivir and control groups, respectively. In the Spinner et al. (2020) study, the rate of withdrawal due to AEs was lower: 2% in the group treated with remdesivir for 10 days, 1% in the group treated with remdesivir for 5 days, and 2% in the SOC group. In the CARAVAN study, 1 patient (8.3%) withdrew due to AEs.

Mortality is discussed in the Mortality section in Efficacy Results.

Critical Appraisal

This review included 5 clinical trials: 4 were RCTs and 1 was a single-arm study. Of the 4 RCTs, 2 were double-blind (ACTT-1 and Wang et al. [2020]). The WHO Solidarity and Spinner et al. (2020) studies were open label and have an elevated risk of bias regarding subjective outcomes and potential for different treatment decisions by clinicians, which was observed in some studies (i.e., patients in the control arm were more likely to receive other putative treatments for COVID-19).

The authors of the WHO Solidarity study criticized the balance of the ACTT-1 treatment groups and suggested that patients with a “good prognosis” (i.e., unventilated at baseline) were overrepresented in the remdesivir group compared to the placebo group of the ACTT-1 study. Patients with an ordinal score of 5, which represented those hospitalized and requiring supplemental oxygen (but not high-flow oxygen or ventilation) in the ACTT-1 study, formed the largest subgroup in the study overall; 43% of the remdesivir group and 39% of the placebo group fit into this category. Notably, the clinical expert consulted by CADTH did not feel this was an important difference in terms of risk of bias. Subgroup results for outcomes related to clinical recovery in the ACTT-1 study demonstrated that only the subgroup of patients who were hospitalized and required supplemental oxygen (but not high-flow oxygen or ventilation) showed a benefit of remdesivir over placebo in contrast to any other clinical status subgroup (i.e., patients not requiring any oxygen support, patients requiring high-flow oxygen or noninvasive ventilation, and patients requiring invasive ventilation or ECMO), which each demonstrated no significant benefit in time to recovery. Similarly, results for mortality in ACTT-1 were the strongest in the subgroup of patients who were hospitalized and required supplemental oxygen (but not high-flow oxygen or ventilation). The randomization stratification categories in the ACTT-1 study — “mild-moderate” and “severe” — were broad, the latter of which hypothetically encompassing patients from all reported ordinal score subgroups (i.e., all levels of oxygen support requirements) by definition.

The results of the WHO Solidarity study demonstrated a benefit in mortality for the subgroup of patients who were already on oxygen (low or high flow but not ventilated). Because the ACTT-1 and WHO Solidarity studies differed regarding which subgroup contained patients on high-flow oxygen, it is uncertain whether there is a benefit of remdesivir in these patients or if the apparent benefit is driven entirely by patients on low-flow oxygen. When patients on high-flow oxygen were grouped with those receiving noninvasive ventilation in the ACTT-1 study, there was uncertainty in the benefit of remdesivir on mortality in this subgroup, but when patients on high-flow oxygen were grouped with those on low-flow oxygen in the WHO Solidarity study, there was an apparent benefit of remdesivir on mortality in this subgroup. Cconsidering these results, the subgroup of patients who received low-flow oxygen — and maybe also those receiving high-flow oxygen although this was inconsistent between the studies — was both the largest subgroup and the 1 most likely to benefit from treatment with remdesivir, at least in time to recovery or clinical improvement (ACTT-1) and mortality (both ACTT-1 and WHO Solidarity) . As such, the imbalance between groups in the ACTT-1 study may be clinically important and may bias the results in favour of remdesivir. The larger WHO Solidarity study confirms the findings of these subgroups in ACTT-1.

The included studies were all conducted in the early stages of the COVID-19 pandemic. There are substantial concerns regarding the external validity and generalizability of all studies included in this review because of the fast-evolving nature of the pandemic and the virus itself. The prevalent variants, vaccination statuses, and clinical outcomes currently are substantially different than those observed in the early pandemic. In consultation with the clinical expert, it was highlighted that the need for remdesivir is infrequent because relatively few patients are presenting with COVID-19 severe enough to warrant hospitalization, and the profile of patients at highest risk for hospitalization and death may have changed. The clinical expert expressed that the difference in variants and vaccination status are both critically important and undermine the ability to generalize results from these trials to a current population.

In addition, background care and SOC were often rarely defined; therefore, it is uncertain whether these are representative of the current patient population of interest.

Long-Term Extension Studies

No long-term extension studies were submitted.

Indirect Comparisons

No indirect comparisons were submitted.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The sponsor noted the following gaps in the submitted evidence: limited evidence on the efficacy and safety of remdesivir in a real-world setting, patients who are immunocompromised, patients discharged after hospitalization for COVID-19, patients with post–COVID-19 condition, patients with renal disease, hospitalized patients treated with remdesivir in combination with dexamethasone, and patients who are vaccinated and not hospitalized as well as across different SARS-CoV-2 variants.

To strengthen the totality of the evidence for remdesivir and address the evidence gaps, the sponsor submitted 9 real-world observational studies: Boglione et al. (2022), Finn et al. (2022), Garibaldi et al. (2021), Kikuchi et al. (2021), Mozaffari et al. (October 2023), Mozaffari et al. (December 2023), Mozaffari et al. (2024), Seethapathy et al. (2022), and Seethapathy et al. (2023).

The study by Mozaffari et al. (October 2023) was a retrospective cohort study that examined the effect of remdesivir on mortality in hospitalized patients with COVID-19 who required supplemental oxygen, including low-flow oxygen, high-flow oxygen or noninvasive ventilation, or invasive mechanical ventilation or ECMO across variant of concern (VOC) periods in a large US health care network. The outcome of this study was 14- and 28-day mortality.

The Mozaffari et al. (2024) study (N = 440,601) was a retrospective study evaluating the effect of remdesivir in adult patients discharged for COVID-19 after hospitalization for COVID-19 on 30-day COVID-19–related and all-cause readmission across different variants and time periods.

The study by Finn et al. (2022) (N = 2,062) was a retrospective study evaluating remdesivir in patients discharged after hospitalization for COVID-19. Outcomes for this study were length of hospital stay, 30-day readmission, and postdischarge 30-day all-cause mortality.

The Boglione et al. (2022) study (N = 449) was a prospective study that aimed to analyze the prevalence and risk factors of post–COVID-19 condition (referred to as "long COVID syndrome" in the study) in patients hospitalized for COVID-19. The study included patients hospitalized at a single hospital in Italy, where they were followed for at least 6 months after discharge.

The Kikuchi et al. (2021) study (N = 1,010) was a registry study evaluating risk factors for mortality in patients receiving dialysis and hospitalized for COVID-19.

The Seethapathy et al. (2022) study (N = 62) was a retrospective cohort study that examined the association between remdesivir and AEs in patients hospitalized for COVID-19 and with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 within the Mass General Brigham health care system located in the Boston, Massachusetts, region in the US. The Seethapathy et al. (2023) study (N = 350) was a retrospective study evaluating the safety of remdesivir in patients hospitalized for COVID-19 and with an eGFR between 15 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2 on adverse kidney outcomes within the Mass General Brigham health care system located in the Boston, Massachusetts, region in the US.

The Mozaffari et al. (December 2023) study (N = 28,338) was a retrospective cohort study that examined the effect of remdesivir on 14- and 28-day mortality in hospitalized patients with COVID-19 and who were immunocompromised across different levels of oxygen requirements and different VOC periods in a large US health care network.

The Garibaldi et al. (2021) study (18,328 pairs of patients receiving remdesivir and not receiving remdesivir) was a retrospective study that included a sensitivity analysis of remdesivir plus dexamethasone versus dexamethasone alone in patients hospitalized for COVID-19 across different VOCs. The outcomes of this study were time to improvement and time to death.

Results

Mozaffari et al. (October 2023)

In the group that received low-flow oxygen, 4,315 (6.4%) patients who received remdesivir and 5,918 (8.8%) matched patients who did not receive remdesivir died within 14 days. By 28 days, 6,641 (9.8%) from the remdesivir group and 8,305 (12.3%) from the matched group that did not receive remdesivir had died across VOC periods. The 14- and 28-day in-hospital mortality (adjusted hazard ratio [aHR]) in patients requiring low-flow oxygen across VOC periods for the remdesivir group compared to the group that did not receive remdesivir was 0.72 (95% CI, 0.66 to 0.79) and 0.79 (95% CI, 0.73 to 0.85), respectively. Estimates were adjusted for covariates, which included age, admission month, admission venue (ICU versus general ward), and baseline concomitant COVID-19 treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab).

In the patients who received high-flow oxygen or noninvasive ventilation, 5,853 (16.8%) patients who received remdesivir and 6,770 (19.4%) who did not receive remdesivir died within 14 days. By 28 days, 9,009 (25.8%) from the remdesivir group and 9,853 (28.3%) from the group that did not receive remdesivir had died. After adjustment for covariates, the 14- and 28-day in-hospital mortality aHR among patients requiring high-flow oxygen or noninvasive ventilation across VOC periods in the remdesivir group) compared to the group that did not receive remdesivir was 0.83 (95% CI, 0.77 to 0.89) for the 14-day in-hospital mortality and 0.88 (95% CI, 0.82 to 0.93) for the 28-day in-hospital mortality.

In the invasive mechanical ventilation or ECMO group, 1,157 (27.8%) patients who received remdesivir and 1,470 (35.3%) patients who did not receive remdesivir died within 14 days. By 28 days, 1,724 (41.4%) from the remdesivir group and 2,105 (50.6%) from the group that did not receive remdesivir had died. After adjustment for covariates, the 14- and 28-day in-hospital mortality aHR for patients requiring invasive mechanical ventilation or ECMO across VOC periods in the remdesivir group compared to the group that did not receive remdesivir was 0.73 (95% CI, 0.65 to 0.82) and 0.74 (95% CI, 0.67 to 0.82), respectively.

Mozaffari et al. (2024)

The remdesivir group had a 30-day COVID-19–related readmission rate of 3.0% and an all-cause readmission rate of 6.3%; for the group that did not receive remdesivir, these were 5.4% and 9.1%, respectively. After adjusting for demographics and clinical characteristics, the odds ratio (OR) of 30-day COVID-19–related readmission and all-cause readmission for the remdesivir-treated group were 0.60 (95% CI, 0.58 to 0.62) and 0.73 (95% CI, 0.72 to 0.75), respectively. Similar ORs for 30-day readmission were observed across all variant time periods in patients treated with remdesivir.

Finn et al. (2022)

Remdesivir treatment was associated with a longer length of hospital stay with a 3.27-day average increase compared to patients who were not treated with remdesivir (95% CI, 2.11 to 4.44 days). This effect was most pronounced in patients with severe COVID-19 symptoms; the increase in length of stay for this group was 6.70 days, but the 95% CIs crossed the null (95% CI, 0.47 to 12.92), compared to patients with mild or moderate symptoms, who had 2.03 days of hospital stay (95% CI, 0.66 days to 3.39 days) in patients

with mild symptoms, and 1.49 days of hospital stay (95% CI, -0.06 days to 3.05 days) in patients with moderate symptoms.

Overall, patients treated with remdesivir had a 19% reduced risk of being readmitted to the hospital within 30 days, but the 95% CI crossed the null (95% CI, 0.59 to 1.13). This reduction in readmission risk was pronounced in patients with mild COVID-19 symptoms; they were 69% less likely to be readmitted if they received remdesivir (RR = 0.31; 95% CI, 0.13 to 0.75).

Remdesivir treatment was associated with a 35% decrease in the risk of dying within 30 days of being discharged from the hospital (HR = 0.65; 95% CI, 0.49 to 0.85).

Boglione et al. (2022)

After multivariate adjustment considering the principal baseline parameters, ICU admission (OR = 2.551; 95% CI, 1.998 to 6.819; P = 0.019), time of hospitalization (OR = 2.255; 95% CI, 1.018 to 6.992; P = 0.016), and treatment with remdesivir (OR = 0.641; 95% CI, 0.413 to 0.782; P < 0.001) were independent predictors of post–COVID-19 condition. Treatment with remdesivir led to a 35.9% rate reduction for post–COVID-19 condition in follow-up.

At visit 1, 123 patients who received remdesivir were not affected by post–COVID-19 condition versus 81 patients who did not receive remdesivir. 27 patients who received remdesivir versus 120 patients who did not receive remdesivir had a post–COVID-19 functional status (PCFS) score of 2 to 3; 13 patients who received remdesivir versus 85 patients who did not receive remdesivir had a PCFS score greater than 3. All differences in the 2 groups were statistically significant (P < 0.001).

Survival analysis comparing the patients treated with remdesivir with the patients who did not receive remdesivir according to the diagnosis of post–COVID-19 condition in the follow-up showed a significant difference between the 2 groups (x^2 = 14.614; P < 0.001).

Kikuchi et al. (2021)

In the multivariate analysis, HR for mortality risk was 4.92 (95% CI, 3.10 to 7.80) for patients aged 70 years or older and 1.58 (95% CI, 0.90 to 2.77) for patients in their 60s. Mortality increased with a longer duration of dialysis. The HR for patients with peripheral arterial disease was 1.49 (95% CI, 1.05 to 2.10). Regarding COVID-19 treatments, mortality was lower in patients who were treated with remdesivir (HR = 0.60; 95% CI, 0.37 to 0.98).

Data from 392 patients were analyzed; of these, 98 patients were treated with remdesivir and matched with 298 patients not treated with remdesivir. The HR for overall survival was 0.45 (95% CI, 0.26 to 0.80) indicating that the overall survival was significantly prolonged in the patient group who were treated with remdesivir than in the patient group who were not treated with remdesivir. The mean duration of hospitalization was 20.9 days (SD = 13.2 days) in the patient group who were treated with remdesivir and 16.2 days (SD = 8.1 days) in the patient group who were not treated with remdesivir (difference = 4.7 days; 95% CI, 2.2 to 7.4 days).

Seethapathy et al. (2022)

Of the patients who were not on dialysis before initiating remdesivir, 1 developed worsening kidney function (defined as ≥ 50% increase in creatinine or initiation of kidney replacement therapy) compared to 3 in the historical control group.

There were no significant differences in the number of AEs between the matched groups, with the exception of an increased risk of hyperglycemia (glucose > 200 mg/dL), which occurred in 81% of patients in the remdesivir-treated population and 55% of the control group (P = 0.03). No significant differences were observed between the 2 groups in lowest hemoglobin or peak alanine transaminase (ALT) values; only peak glucose was significantly different. In-hospital creatinine trajectories among patients treated with remdesivir patients, 1 patient met the predefined criteria for worsening kidney function due to initiation of kidney replacement therapy. Among the control group not treated with remdesivir, 3 patients experienced a greater than 50% increase in serum creatinine.

Early discontinuation of remdesivir occurred in 4 patients (14%) due to safety concerns regarding elevated transaminase levels and low eGFR. The overall mortality rate during the hospital stay was 19% (n = 6) in patients treated with remdesivir and 23% (n = 7) in the control group not treated with remdesivir (P = 0.71).

Seethapathy et al. (2023)

Mean peak creatinine was 2.3 mg/dL (95% CI, 1.98 mg/dL to 2.57 mg/dL) and 2.5 mg/dL (95% CI, 2.13 mg/dL to 2.89 mg/dL) in the remdesivir-treated group and matched untreated historical comparators, respectively. Sensitivity analysis only included patients who received a full course of remdesivir and those with at least 5 posttreatment creatinine measurements.

A total of 18 patients treated with remdesivir (10.3%) and 23 untreated historical comparators (13.1%) experienced doubling of serum creatinine during hospitalization.

Of the patients treated with remdesivir, 8 (4.6%) received kidney replacement therapy during their hospitalization compared to 11 (6.3%) in the matched untreated historical comparator group.

A total of 120 surviving patients who were followed for at least 90 days post admission, the average eGFR at day 90 was 54.7 mL/min/1.73 m^2 (SD = 20.0 mL/min/1.73 m^2) for patients treated with remdesivir (n = 66) compared to 51.7 mL/min/1.73 m^2 (SD = 19.5 mL/min/1.73 m^2) for the untreated historical comparator group (n = 54).

Mozaffari et al. (December 2023)

Unadjusted mortality rates were lower among patients who received remdesivir compared with patients who did not receive remdesivir across all VOC periods and all levels of baseline supplemental oxygen requirement. Among the remdesivir group, 11.1% of patients died within 14 days and 17.7% died within 28 days. In the group that did not receive remdesivir, 15.4% of patients died within 14 days and 22.4% died within 28 days. After adjusting for baseline and clinical covariates, HR for mortality risk in the remdesivir group on admission was 0.70 (95% CI, 0.62 to 0.78) at day 14 and 0.75 (95% CI, 0.68 to 0.83) at day 28. Similar results were seen during each VOC period and were most pronounced during the pre-Delta period

at the 14-day assessment; the HR for pre-Delta was 0.59 (95% CI, 0.48 to 0.71), Delta was 0.77 (95% CI, 0.65 to 0.92), and Omicron was 0.75 (95% CI, 0.63 to 0.90). At 28 days, the HR for the pre-Delta, Delta, and Omicron periods were 0.65 (95% CI, 0.56 to 0.76), 0.79 (95% CI, 0.68 to 0.91), and 0.84 (95% CI, 0.72 to 0.97), respectively.

For subgroups of patients without supplemental oxygen charges in hospitals documented to charge for supplemental oxygen (NSOc) on admission within the remdesivir group, the HR for mortality was 0.71 (95% CI, 0.58 to 0.87) and 0.78 (95% CI, 0.66 to 0.93) at days 14 and 28, respectively. For those who required low-flow oxygen on admission, HR for mortality was 0.56 (95% CI, 0.46 to 0.68) and 0.62 (95% CI, 0.53 to 0.72) at days 14 and 28, respectively. The HR among those who required high-flow oxygen or noninvasive ventilation or invasive mechanical ventilation or ECMO on admission was 0.83 (95% CI, 0.70 to 0.99) and 0.86 (95% CI, 0.75 to 0.99) at days 14 and 28, respectively.

Garibaldi et al. (2021)

Of 36,656 matched patients, 13,569 (74.0%) in the remdesivir group and 12,510 (68.3%) in the group that did not receive remdesivir achieved clinical improvement before 28 days, with a median time to clinical improvement of 7 days (IQR, 5 to 19 days) in the remdesivir group and 9 days (IQR, 5 to 28 days) in the group that did not receive remdesivir. The aHR for clinical improvement at 28 days for the remdesivir group was 1.19 (95% CI, 1.16 to 1.22). The aHR for clinical improvement for the remdesivir patients receiving no oxygen was 1.30 (95% CI, 1.22 to 1.38) with a median of 5 days (IQR, 4 to 13 days) for the remdesivir group compared to 7 days (IQR, 5 to 15 days) for the control group.

The aHR for clinical improvement among patients receiving remdesivir on low-flow oxygen was 1.23 (95% CI, 1.19 to 1.27), with a median of 6 days (IQR, 4 to 11 days) for the remdesivir group compared to 7 days (IQR = 5 to 15) in the control group. The aHR for clinical improvement among patients receiving remdesivir on high-flow nasal cannula and noninvasive positive pressure ventilation was 0.95 (95% CI, 0.89 to 1.01) for high-flow nasal cannula and noninvasive positive pressure ventilation, with a median of 15 days (IQR, 7 to 28 days) compared to 17 days (IQR, 8 to 28 days) in the control group. The aHR for clinical improvement for patients receiving remdesivir on invasive mechanical ventilation at the time of initiation remdesivir also was 0.92 (95% CI, 0.81 to 1.04) for invasive mechanical ventilation, with a median of 28 days (IQR, 10 to 28 days) in the remdesivir group compared to 28 days (IQR, 9 to 28 days) in the control group.

There was no significant impact of remdesivir on mortality overall, with an aHR of 1.02 (95% CI, 0.97 to 1.08) and 28-day mortality of 15.7% (2,879 deaths) for the remdesivir group compared to 19.6% (3,586 deaths) for the matched control group.

For patients on room air, the aHR for mortality was 1.08 (95% CI, 0.92 to 1.27) and 28-day mortality was 11.4% (325 deaths) for the remdesivir group compared to 13.3% (329 deaths) for the matched control group. The aHR for patients treated with remdesivir on low-flow oxygen was 0.85 (95% CI, 0.77 to 0.92) and 28-day mortality was 8.4% (865 deaths) compared to 12.5% (1,334 deaths) for the matched control groups.

For the patients treated with remdesivir on high-flow nasal cannula or noninvasive positive pressure ventilation, the aHR for mortality was 1.10 (95% CI, 1.01 to 1.20) and 28-day mortality was 28.6% (1,137

deaths) compared to 34.0% (1,237 deaths) for the matched control group. For patients treated with remdesivir on invasive mechanical ventilation, the aHR for mortality was 1.17 (95% CI, 1.04 to 1.32) and 28-day mortality was 46.7% (552 deaths) compared to 43.9% (686 deaths) for the matched control groups.

The aHR for clinical improvement by day 28 in the group who received remdesivir plus dexamethasone versus the group who received dexamethasone alone in the overall patient population was 1.21 (95% CI, 1.18 to 1.25). For patients on room air and on low-flow oxygen, aHR for clinical improvement was 1.31 (95% CI, 1.23 to 1.41) and 1.24 (95% CI, 1.20 to 1.28), respectively. Regarding survival benefits, the aHR in the remdesivir plus dexamethasone group versus dexamethasone alone group in patients on low-flow oxygen was 0.83 (95% CI, 0.76 to 0.91).

Critical Appraisal

Guidance for Reporting Real-World Evidence is the foundation for transparent reporting of RWE studies in Canada and facilitates appraisals of RWE by CADTH. All applicable sections in the guidance should be reported when the sponsor submits RWE studies as part of a Reimbursement Review. Many RWE studies submitted as part of this review were missing important information. Information about why they did not choose a setting in Canada; and how differences in health systems, access to care, available health care resources during the pandemic, and other factors that may impact the care of patients with COVID-19 might affect applicability of findings to the current Canadian context, was missing. A detailed description of data specifications (access, cleaning, and linkage where applicable), data sources, including a data dictionary and variables that could not be captured and their potential impact on study results were not provided.

The pivotal trial data lack information regarding the effect of remdesivir on mortality for more recent variants of SARS-Cov-2. A large observational study by Mozaffari et al. (October 2023) found that treatment with remdesivir reduced 14- and 28-day mortality compared to no treatment with remdesivir in patients who were hospitalized for COVID-19 between December 2020 and April 2022. The study by Mozaffari et al. (October 2023) may address a gap in the pivotal trial data because it describes comparative effectiveness of remdesivir on the outcomes of 14- and 28-day mortality in a population of patients across 3 variants (pre-Delta, Delta, and Omicron). Limitations included lack of information about time of symptom onset, treatments, and vaccines administered before hospitalization. Although many comorbidities were controlled for, there remains potential for imbalances in unmeasured confounders and residual confounding. Similarly, a large observational study by Mozaffari et al. (2024) found that treatment with remdesivir reduced 30-day all-cause and COVID-19–related rehospitalizations compared to no treatment with remdesivir in patients who were hospitalized between December 2020 and April 2022 across 3 variants (pre-Delta, Delta, and Omicron). Limitations include that the impact of missing data on the outcome of rehospitalization is not clear. There is also a lack of information about time since symptom onset and treatments received before hospitalization. Despite inclusion of numerous variables in the multivariate regression, there is still potential for unmeasured confounders. For both the Mozaffari et al. (October 2023) and Mozaffari et al. (2024) studies, it is unclear whether the information from the US cohort is generalizable to Canada. Vaccine uptake, background disease risk, and the circulating variants have changed, which may limit the generalizability of these findings to the current COVID-19 treatment landscape. Therefore, it is challenging to assess the exact magnitude of

treatment effect of remdesivir on reduction of in-hospital 14- and 28-day mortality compared with patients who were not treated with remdesivir and to extrapolate the effect to current practice in Canada.

The pivotal trial data lack clear information about the effect of remdesivir on outcomes that occur after hospital discharge. The study by Finn et al. (2022) was a small observational study (742 treated with remdesivir matched to 1,539 not treated with remdesivir) that used electronic health records data from 3 hospitals in Rhode Island in the US. This study found that the group of patients that received remdesivir had lower hospital readmission rates and 30-day all-cause mortality compared to no remdesivir in patients who were discharged from being hospitalized for COVID-19 between April 2020 and December 2020. The study by Finn et al. (2022) may address a gap in the pivotal trial data; however, it is subject to numerous limitations. Limitations include a lack of information about time since symptom onset, potential for time-related bias in assessment of hospitalization, potential for missing data related to postdischarge outcomes, as well as potential for unmeasured confounders and residual confounding. Therefore, it is challenging to assess the exact magnitude of benefit of remdesivir from this study on outcomes that occur after discharge from hospital for patients hospitalized with COVID-19 and to extrapolate the effect to current practice in Canada.

The pivotal trial data lack clear information about the effect of remdesivir on post–COVID-19 condition. The study by Boglione et al. (2022) is a small (including 163 treated with remdesivir) observational study of patients with COVID-19 who were hospitalized at a single hospital in Italy from March 2020 to January 2021. The Boglione et al. (2022) study likely has significant methodologic limitations, including risks for confounding by indication and lack of matching, uncertainty in the outcome definition of post–COVID-19 condition, and limited generalizability from the Italian setting to Canada. These limitations preclude drawing conclusions about the effect of remdesivir on post–COVID-19 condition from this study.

The pivotal trial data lack clear information about the effect of remdesivir in patients with renal insufficiency. Three RWE studies were submitted to address this, including the studies by Kikuchi et al. (2021), Seethapathy et al. (2021), and Seethapathy et al. (2023). The study by Kikuchi et al. (2021) was a small observational study (98 treated with remdesivir matched to 294 not treated with remdesivir) that used registry data to assess the effect of remdesivir on mortality in patients admitted to hospital with COVID-19 and receiving dialysis in Japan from April 2020 to June 2021. The study by Seethapathy et al. (2021) was a small observational study (31 treated with remdesivir matched with 31 not treated with remdesivir) that used data from a single US hospital to examine the relationship between treatment with remdesivir in patients with an eGFR less than 30 mL/min/1.73 m^2 and AEs (from May 2020 to January, 2021 for those treated with remdesivir and March and April 2020 for those not treated with remdesivir). The study by Seethapathy et al. (2023) was a small observational study (175 treated with remdesivir matched with 175 not treated with remdesivir) that used data from a single US hospital to examine the relationship between treatment with remdesivir in patients with an eGFR from 15 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2 and adverse laboratory-based renal outcomes (from April 2020 to November 2020 for those treated with remdesivir and March and April 2020 for those not treated with remdesivir). Limitations to all 3 studies and the inability to extrapolate the effect to current practice in Canada preclude conclusions about the effect of remdesivir in patients admitted to hospital with COVID-19 and receiving dialysis or with reduced renal function.

The pivotal trial data lack clear information about the effect of remdesivir in patients who are immunocompromised. The study by Mozaffari et al. (December 2023) was a large observational study (14,169 treated with remdesivir matched with 14,169 not treated with remdesivir) that used a US dataset. The study found that remdesivir reduced 14- and 28-day mortality in patients who were immunocompromised and hospitalized for COVID-19 between December 2020 and April 2022 compared to those patients who did not receive remdesivir. The Mozaffari et al. (December 2023) study may address a gap in the pivotal trial data because it describes the comparative effectiveness of remdesivir on the outcomes of 14- and 28-day mortality in patients who are immunocompromised. Limitations included lack of information about time of symptom onset, treatments, and vaccines administered before hospitalization. Although many comorbidities were controlled for, there remains a potential for imbalances in unmeasured confounders. It is difficult to extrapolate the magnitude of effect of treatment for patients who are immunocompromised in Canada due to uncertainty about the generalizability of the US cohort to Canada.

Results from the study by Garibaldi et al. (2021) were submitted by the sponsor to address the effect of remdesivir in patients receiving dexamethasone. This study was a large (18,328 pairs of patients treated with remdesivir and patients not treated with remdesivir) observational study that used a US dataset to examine the relationship between remdesivir exposure on time to improvement in patients who were hospitalized with COVID-19 from February 2020 to February 2021. The Garibaldi et al. (2021) study may address a gap in the pivotal trial data; however, the analysis of remdesivir plus dexamethasone compared with no remdesivir on time to improvement is based on a sensitivity analysis only and, therefore, has limitations. Additional limitations include the potential for information bias due to the subjective nature of time to improvement (2-point decrease in the WHO severity score or discharged alive without worsening of WHO severity score within 28 days), lack of information about time since symptom onset, or treatments received before hospitalization. Approximately half of the patients treated with remdesivir were unable to be matched, which is a potential source of bias; potential for unmeasured confounders and residual confounding are other limitations. It is unclear whether the information from the US cohort is generalizable to Canada. Vaccine uptake, background disease risk, and circulating variants have changed, which may limit the generalizability of these findings to the current COVID-19 treatment landscape. Therefore, it is challenging to assess the exact magnitude of the treatment effect of remdesivir on time to improvement compared with patients not treated with remdesivir and to extrapolate the effect to current practice in Canada.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Hospitalized patients with COVID-19 requiring supplemental oxygen
Treatment	Remdesivir
Dose regimen	Adult and pediatric patients (weighing at least 40 kg): 200 mg on day 1, followed by 100 mg once daily for an additional 4 to 9 days (for a total treatment duration of 5 to 10 days)
Submitted price	Remdesivir 100 mg vial: $660.53 per vial
Submitted treatment cost	$3,963.18 per patient, based on a 5-day treatment duration
Comparator	SOC comprising a combination of dexamethasone and therapeutic anticoagulation in some cases
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	6 weeks
Key data sources	ACTT-1 trial Real-world evidence (Mozaffari et al. [October 2023])
Key limitations	• The population in the ACTT-1 trial does not accurately reflect the population at risk for progression to severe COVID-19 in the current setting in Canada. This is due to higher vaccination rates and the emergence of the Omicron variant of SARS-CoV-2, which was not present at the time of the ACTT-1 trial. These differences represent a fundamental challenge in interpreting the results from the sponsor's submitted evidence dossier and accompanying pharmacoeconomic model based on the ACTT-1 trial. • The mortality benefit for patients treated with remdesivir, as estimated by a sponsor-conducted observational study, is highly uncertain due to internal and external validity concerns. • The level of care patients require upon hospital admission was informed by the ACTT-1 trial and does not accurately reflect the current 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	• CADTH conducted several reanalyses after adjusting the baseline distribution for level of hospital care and COVID-19 hospitalization costs. CADTH's reanalyses focused on alternative mortality benefit assumptions for treatment with remdesivir compared to SOC. • Results of CADTH's reanalyses ranged from remdesivir having an ICER of $2,542,952 per QALY gained to $4,208,181 per QALY gained compared to SOC. The incremental costs of remdesivir were similar in all CADTH reanalyses (approximately $3,600); the incremental QALYs ranged from 0.0014 to 0.0009. A price of $317 to $396 per 5-day treatment course (a reduction of approximately 90% to 92%) would be required for remdesivir to be considered cost-effective at a threshold of $50,000 per QALY gained, depending on assumptions about the mortality benefit for patients treated with remdesivir.

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

Note: The dose regimen for pediatric patients aged at least 4 weeks old (weighing at least 3 kg but less than 40 kg) is 5 mg/kg on day 1 followed by 2.5 mg/kg daily for up to an additional 9 days (for a total treatment duration of up to 10 days).

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: The eligible population size is uncertain, and treatment costs may be underestimated. CADTH reanalyses revised the annual number of hospitalizations. In the CADTH base case, 3-year budget impact of reimbursing remdesivir for hospitalized patients with COVID-19 aged 12 years and older (weighing at least 40 kg) with pneumonia requiring supplemental oxygen is estimated to cost $58,058,334 ($19,352,778 in each of year 1, year 2, and year 3). The estimated budget impact is highly sensitive to the duration of treatment with remdesivir and the number of patients hospitalized because of COVID-19 and expected to be treated for COVID-19.

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: One expert committee member did not attend.

Conflicts of interest: None

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