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 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.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that remdesivir be reimbursed for the treatment of COVID-19 in hospitalized patients ≥ 12 years of age (weighing at least 40 kg) with pneumonia requiring supplemental oxygen only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

Findings from 4 RCTs (ACTT-1, WHO Solidarity, Spinner et al. [2020], and Wang et al. [2020]) conducted during the early COVID-19 pandemic in 2020 suggested that remdesivir may prevent death in hospitalized patients aged at least 12 years with COVID-19 where 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. Additionally, remdesivir may be associated with a benefit in the incidence of new ventilation support among patients not ventilated at baseline. However, impact on the duration of hospitalization are 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 modern-day and future severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants.

The clinical 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. CDEC noted that remdesivir may prevent death in hospitalized patients where 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 to treat COVID-19 in hospitalized patients ≥ 12 years of age (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 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 and weighing at least 40 kg with confirmed COVID-19 infection requiring supplemental oxygen due to COVID-19 infection but not ventilation.	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 and weighed at least 40 kg if aged 12 to <18. Subgroup analyses in ACTT-1 and WHO Solidarity demonstrated that remdesivir was associated with clinical benefit, including reduced mortality, specifically amongst the subgroup of patients who were receiving supplemental oxygen at baseline.	The reason for requiring supplemental oxygen should be directly attributable to the symptoms of COVID-19 infection, and not due to comorbid conditions.
2. Treatment with remdesivir must not be reimbursed when initiated in patients with any of the following:	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	—

Reimbursement condition	Reason	Implementation guidance
2.1. receiving mechanical ventilation 2.2. receiving extracorporeal membrane oxygenation 2.3. on room air, not requiring oxygen support	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 omicron 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; WHO = World Health Organization.

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 severe enough disease to require supplemental oxygen or organ support due to COVID-19, but not those who have already progressed to ventilation prior to the initiation of remdesivir. The clinical expert consulted agreed with this recommendation but noted to CDEC that, as the virus evolves, this could change in the future. As 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 direct body of evidence due to the rapidly changing nature of COVID-19. All of 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, at that time there was not widespread access to COVID-19 vaccinations, and population immunity and risk factors for progression to severe disease all differed. CDEC discussed that the severity of COVID-19 infection and the likelihood of hospitalization and death directly related to COVID-19 in the present day are substantially lower 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, e.g., 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 healthcare 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 for the potential future wherein the risks associated with COVID-19 outbreaks could increase again.
- Based on the Health Canada recommended dosage, the duration of treatment with remdesivir in hospitalized patients over 12 years of age and weighing 40 kg is a minimum of 5 days up to a maximum of 10 days. While most evidence evaluated 10-day regimens, 1 RCT compared both 5-day and 10 day-regimens to control, and there was no additional benefit or harm of the longer regimen. CDEC discussed that in 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 with regards to where high-flow oxygen was categorized, so there is uncertainty regarding whether patients on high-flow oxygen similarly benefit as patients receiving low-flow oxygen support. The largest included study, WHO Solidarity, grouped high-flow and low-flow oxygen together in 1 subgroup. CDEC concluded that extending reimbursement to patients on high-flow oxygen was prudent as a result.
- CDEC also evaluated evidence from several real-world observational studies submitted to address gaps in the evidence provided by pivotal studies, including efficacy and/or safety of remdesivir in immunocompromised patients, 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, combination with dexamethasone among hospitalized patients, and vaccinated non-hospitalized patients, and 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 which 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 four reanalyses conducted by CADTH that used different assumptions for the mortality benefit for remdesivir. Based on the clinical evidence, which indicated that 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, 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 the World Health Organization on March 11, 2020. Subsequently, the proliferation of COVID-19 has presented significant challenges to healthcare 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%. From April 2022 to March 2023 in Canada according to the Canadian Institute for Health Information, there were 120,524 hospitalizations due to COVID-19, compared to the year before where there were 125,986 hospitalizations due to COVID-19. In 2022-2023, of those admitted to hospital, 10% died in the facility and 13% were admitted to the ICU.5 Among those admitted to the ICU, 39% received ventilation. The estimated total cost of COVID-19 hospitalizations in 2022-2023 were ~$2.9 billion, and costs continue to increase each fiscal year.

Patients with symptomatic COVID-19 have a wide range of symptoms ranging from no or mild 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, where individuals experience respiratory failure,

septic shock, and/or various organ dysfunction known to be associated with high morbidity and mortality. Mortality risk estimates reported by the 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 non-hospitalized 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 being hospitalized and dying. For this review, the sponsor has 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 anti-viral medication. It is available as a powder for solution for administration by intravenous infusion and the dosage recommended in the product monograph is 200 mg infusion on day 1 followed by 100 mg infusion daily in adults, or in children, 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 who are not hospitalized and are at increased risk of progressing to severe COVID-19 and weigh at least 40 kg.

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
- 1clinical 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 as a result 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, and an oral delivery of the medication would be ideal. A significant treatment goal is also 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, as the majority of evidence was generated with early variants and may not apply.

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 agent based on the WHO living guidance for clinical management of COVID-19. It was also noted that remdesivir is unique in its antiviral action, as unlike other therapies for COVID-19, it does not target host immune response. The clinical expert stated that remdesivir would not change clinical practice as it is rarely used since the early stages of the pandemic.

Among inpatients, those most in need of an intervention are those at risk of death. Diagnosis of COVID-19 is based on polymerase chain reaction (PCR; 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 as the available data primarily evaluates early pandemic SARS-CoV-2 variants and largely unvaccinated patient populations. However, the expert described that it may be the case that patients who are sick enough to require oxygen support as a result of COVID-19, but 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 and so there are serious limitations regarding the generalizability of the results. Nonetheless, speculatively, the expert discussed 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, ergo 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 (among patients already admitted to hospital) are oxygen/organ support and rate of mortality. Meaningful response would be a change in status of oxygen or organ support requirements, and this does not vary by physician interpretation as they are objective outcomes. Clinical symptoms and viral load are not relevant clinical outcomes and they 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 per day 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.Inpatient treatment with remdesivir would be prescribed 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 corticosteroid, which is recommended as first-line treatment for hospitalized adults with COVID-19 requiring any supplemental oxygen, Janus kinase inhibitor, and anti-interleukin (IL)-6 receptor monoclonal antibody. Remdesivir can be added to other immunomodulatory agents which work on the hyperinflammatory pathway that tends to drive 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, non-invasive ventilation (e.g., 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 some limitations with remdesivir, such as the drug formulation (IV), and lack of randomized controlled trials (RCTs) on the effectiveness of remdesivir on all variants, especially Omicron.

According to the clinician group, hospitalized patients who require supplemental low-flow oxygen are best suited for treatment with remdesivir. 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, intensive care unit [ICU] admission, ICU length of stay, time to improvement in clinical status, progression to high flow oxygen or non-invasive ventilation, progression to mechanical ventilation or extracorporeal membrane oxygenation, time to receipt of mechanical ventilation, time to clinical improvement, mortality, length of hospital stay, serious adverse events, withdrawals from study due to adverse event, etc).

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

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:

- 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 see appreciable benefit? E.g., consider: • Need for supplemental oxygen • Use of high-flow nasal cannula oxygen • Use of non-invasive 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 not sick enough to need oxygen or organ support, and patients that 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. At the moment, these “medium prognosis” patients are those the clinical expert described as those who may need access to remdesivir. However, as the virus evolves, the expert noted that this could change in the future. 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 dose of remdesivir does not otherwise vary (200 mg on the first day followed by 100 mg daily). Because the data does not show a clear benefit or harm of 10 days over 5 days, the clinical expert suggested that the lowest effective duration should be used. However, as 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.

WHO = World Health Organization.

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 = 1062) was a double-blind, placebo-controlled, multi-centre, international, phase 3 RCT in adults aged at least 18 years admitted to hospital with confirmed COVID-19. Wang et al. (2020) (N = 237) was a double-blind, placebo-controlled, multi-centre RCT in conducted in 10 hospitals in China in adult patients aged at least 18 years admitted to hospital with confirmed COVID-19. WHO Solidarity (N = 8320 for remdesivir and its control group) was an open-label, SOC-controlled RCT of several putative treatments for COVID-19 across the globe in adults with definite COVID-19, although only the remdesivir group and its associated control group are described for the purpose of this report. Spinner et al. (2020) (N = 596) was an open-label multi-centre international RCT evaluating 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 2/3, international study in pediatric patients, of which only those in Cohort 1 (N = 12) were at least 12 years of age and 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 intention-to-treat (ITT) population, the risk of death by day 15 was lower in the remdesivir 10-day group 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, 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 percentages of deaths among participants with known mortality status at day 29 in the remdesivir 10-day group compared with that in the placebo group was observed in the subgroup with baseline ordinal score 5 (i.e., patients receiving low-flow oxygen; 4.1% in the remdesivir group [9 of 222 participants] versus 12.8% in the placebo group [25 of 195 participants]; HR [95% CI] = 0.30 [0.14 to 0.64], P <0.001 [without adjustments for multiplicity]) and in the actual severe disease stratum (12.5% in the remdesivir group [57 of 457 participants] versus 16.3% in the placebo group [74 of 453 participants]). Patients with baseline ordinal score 5 also represent by far the most populous subgroup by ordinal score ACTT-1.

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%) of patients died, and in the placebo group, 10 of 78 (13%) of patients 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), but the numerical results differed in direction: in the early use subgroup, mortality was numerically higher in the placebo group, while in the late use subgroup, mortality was numerically higher in the remdesivir group.

In WHO Solidarity, of 8275 patients in the overall remdesivir analyses, 602 (14.5%) of 4146 assigned to remdesivir and 643 (15.6%) of 4129 assigned to controls died (risk ratio [RR] = 0.91 [95% CI: 0.82 to 1.02], P = 0.12). These analyses of in-hospital mortality include 15 palliative discharges in the remdesivir group and 11 in the control group. Analyses were also subdivided by oxygen support requirements at baseline, and 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 10-day remdesivir group (N = 193), 5-day remdesivir group (N = 191), and standard of care (SOC) group (N = 200), a total of 3 (2%), 2 (1%), and 4 (2%) patients died from any cause through 28 days of the trial. The Kaplan-Meier (KM) estimates of all-cause mortality at day 28 were 1% (95% CI: 0.0% to 2.6%, P = 0.43 vs. SOC) for the 5-day remdesivir group, 2% (95% CI 0.0% to 3.6%, P = 0.72 vs. SOC) for the 10-day remdesivir group, and 2% (95% CI 0.1% to 4.1%) for the SOC group.

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

Duration of Hospitalization

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

In contrast, WHO Solidarity reported that allocation to remdesivir delayed discharge by about 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 CARAVAN, the mean duration of hospitalization from day 1 (days from first dose to date discharged alive, n = 9) was 12 days (SD 5.5 days) and the median (IQR; range) was 12 (8 to 15; 6 to 24).

Time to Recovery or Clinical Improvement

Results from ACTT-1 were stratified by disease severity within the ITT population, where “mild-moderate” disease was defined as having a blood oxygen saturation (SpO_2) of more than 94% and respiratory rate of fewer than 24 breaths/minute without supplemental oxygen, and “severe” disease was defined as requiring mechanical ventilation, requiring oxygen, SpO_2 equal or less than 94% on room air, or tachypnea (respiratory rate equal or more than 24 breaths/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) in the remdesivir group and 7 days (95% CI: 5 to 9) in the placebo group (risk of recovery ratio [RRR] = 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) in the remdesivir group versus 19 days (95% CI: 16 to 21) in the placebo group (RRR 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) in the remdesivir group (n = 541), and 15 days (95% CI: 13 to 18) in the placebo group (n = 521). Subgroup analyses were also conducted according to ordinal score at baseline, which was 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, and this was also the most populous subgroup (remdesivir N = 232 and placebo N = 203).

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

In Spinner et al. (2020), comparing the 10-day remdesivir group to the SOC group, there were no significant differences between groups for the time to 2-point 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 5-day remdesivir group to the SOC group, there were also no significant differences between the groups for the time to 2-point 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 (IQR) time to recovery in cohort 1 of CARAVAN was 12 (6, 24) days.

This outcome was not assessed in WHO Solidarity.

Initiation of Ventilation

Only ACTT-1 and WHO Solidarity reported this outcome.

In ACTT-1, the incidence rate (95% CI) of new non-invasive ventilation or high flow oxygen use, among patients who were not already on these supports (nor ventilated) at baseline, was 0.17 (0.13 to 0.22) in the remdesivir group and 0.24 (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 overlap. The

incidence rate (95% CI) of new invasive mechanical ventilation or ECMO use among patients not already on these supports at baseline was 0.13 (0.10 to 0.17) in the remdesivir group and 0.23 (0.19 to 0.27) in the placebo group. The incidence rate in the remdesivir group was numerically lower, and the 95% CIs of each group do not overlap.

In WHO Solidarity, assignment to remdesivir was associated with a lower rate of progression to ventilation (event risk ratio [RR] = 0.88, 95% CI: 0.77 to 1.00, P = 0.04) and with a lower composite outcome of death or ventilation (0.84, 95% CI: 0.75 to 0.93, P = 0.001). For both outcomes, results for the subgroup of patients not receiving 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 of remdesivir. The latter subgroup was also much larger, and 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 sub-study, CATCO, among patients not mechanically ventilated at baseline, 8.0% of those assigned remdesivir required mechanical ventilation during the study, compared to 15.0% of those assigned SOC (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 were summarized. Briefly, ACTT-1 reported the median days on oxygen, non-invasive ventilation or high-flow oxygen, or invasive mechanical ventilation / ECMO; although statistical comparisons were not conducted and the interquartile (IQR) ranges overlapped between groups, the median days on oxygen or invasive mechanical ventilation / 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 non-invasive ventilation / high-flow oxygen. CATCO reported a significant benefit associated with allocation to remdesivir in terms of the mean oxygen-free days and mean 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 again the IQRs overlapped. The study by Spinner et al. (2020) reported no significant difference between either remdesivir group and SOC in the duration of oxygen support. There is therefore 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 of 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 CARAVAN. The studies differed substantially in which particular AEs were reported, but there was a trend across the trials of focus on biomarkers related to kidney and liver function, hyperglycemia, and some clinical AEs such as headache, constipation, pyrexia, and diarrhea, among others. Where 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 serious AE (SAE) ranged from 5% in both remdesivir groups of Spinner et al. (2010) to 32% in the placebo group of ACTT-1. In Cohort 1 of CARAVAN, 5 (41.7%) patients experienced an SAE.

In ACTT-1, there was a substantially higher proportion of patients who experienced SAEs in the placebo arm (32%) than the remdesivir arm (25%). This was also the case in Wang et al. (2020) (26% in the placebo arm versus 18% in the remdesivir arm). In Spinner et al. (2020), in both remdesivir groups – 10 day and 5 day – 5% of patients experienced at least 1 SAE, while in the SOC group, 9% of patients experienced at least 1 SAE. WHO Solidarity did not report this outcome.

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

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

Mortality has been discussed in depth in the *Efficacy* section.

Critical Appraisal

This review included 5 clinical trials, 4 of which were RCTs and one of which was a single-arm study. Of the 4 RCTs, 2 were double-blind (ACTT-1 and Wang et al. [2020]). WHO Solidarity and Spinner et al. (2020), being open label, have an elevated risk of bias with regards to subjective outcomes and the 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 WHO Solidarity criticized the balance of the ACTT-1 treatment groups and suggested that patients with "good prognosis" (i.e., unventilated at baseline) were over-represented in the remdesivir group compared to the placebo group of ACTT-1. Patients with an ordinal score of 5, which in ACTT-1 represents those hospitalized and requiring supplemental oxygen (but not high-flow oxygen or ventilation), formed the largest subgroup in ACTT-1 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 ACTT-1 demonstrated that only the subgroup of patients who are hospitalized and requiring 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 non-invasive 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 are hospitalized and requiring supplemental oxygen (but not high-flow oxygen or ventilation). The randomization stratification categories in ACTT-1, "mild-moderate" and "severe," were broad, the latter of which hypothetically encompassing patients from all reported ordinal score subgroups – or in other words, all levels of oxygen support requirements – by definition.

The results of WHO Solidarity demonstrated a benefit in mortality for the subgroup of patients who were already on oxygen (low or high flow, but not ventilated). As these ACTT-1 and WHO Solidarity differed in which subgroup contains 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 non-invasive ventilation in ACTT-1, 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 WHO Solidarity, there was an apparent benefit of remdesivir on mortality in this subgroup. Taken together, the subgroup of patients receiving low-flow oxygen – and perhaps including those receiving high-flow oxygen, as well, but this was inconsistent between the studies – was both the largest subgroup and the one most likely to benefit, at least in time to recovery or clinical improvement (ACTT-1) and mortality (both ACTT-1 and WHO Solidarity), from treatment with remdesivir. As such, the imbalance between groups in ACTT-1 may be clinically important and may bias the results in favour of remdesivir; while it is otherwise possible the other subgroups were too small to demonstrate a benefit, the larger WHO Solidarity study confirms the findings of these subgroups in ACTT-1.

The included studies were each conducted in the early eras of the COVID-19 pandemic. There are substantial concerns regarding the external validity and generalizability of every study included in this review as a result of the fast-evolving nature of the pandemic and the virus itself, as prevalent variants, vaccination status, and clinical outcomes in today's world 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 as 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.

Additionally, background care and SOC were often sparsely defined, and it is therefore uncertain whether they are representative of those experienced by 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, immunocompromised patients, patients discharged after hospitalization for COVID-19, patients with post–COVID-19 condition, patients with renal disease, combination with dexamethasone among hospitalized patients, and vaccinated non-hospitalized patients, and 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: Mozaffari et al., 2023, Mozaffari et al., 2024, Finn et al., 2022, Boglione et al., 2022, Kikuchi et al., 2021, Seethapathy et al., 2022, Seethapathy et al., 2023, Mozaffari et al., 2023, Garibaldi et al., 2021.

The study by Mozaffari et al., 2023, was a retrospective cohort study that examined the effect of remdesivir on mortality among in-hospital patients with COVID-19 and who required supplemental oxygen, including low-flow oxygen (LFO), high-flow oxygen/noninvasive ventilation (HFO/NIV), or invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO) across variant of concern (VOC) periods in a large US healthcare network on the outcome of 14- and 28-day mortality. Mozaffari et al. 2024 (N = 440, 601) was a retrospective study evaluating the effect of remdesivir among adult patients discharged for COVID-19 during hospitalization for COVID-19 on 30-day COVID-19-related and all-cause readmission across different variants and time periods. Finn A et al. 2022 (N = 2,062) was a retrospective study evaluating remdesivir in patients discharged after hospitalization for COVID-19 for the outcomes of length of hospital stay, 30-day readmission, and post-discharge 30-day all-cause mortality. Boglione L et al. 2022 (N = 449) was a prospective study that aimed to analyze the prevalence and risk factors of Long Covid Syndrome (LCS) 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 post-discharge. Kikuchi K et al. 2021 (N = 1010) was a registry study evaluating risk factors for mortality in patients receiving dialysis and who were hospitalized for COVID-19. Seethapathy R et al., 2022 (N = 62) was a retrospective cohort study that examined the association between remdesivir and adverse events in COVID-19 hospitalized patients with estimated glomerular filtration rate (EGFR) less than 30 mL/min/1.73m^2 within the Mass General Brigham (MGB) health care system located in the Boston, USA region. Seethapathy R et al., 2023 (N = 350) was a retrospective study evaluating the safety of remdesivir in patients hospitalized for COVID-19 and with eGFR between 15 to 60mL/min/1.73m^2 on adverse kidney outcomes. Mozaffari et al. 2023 (N = 28,338) was a retrospective cohort study that examined the effect of remdesivir on mortality among in-hospital patients with COVID-19 and who were immunocompromised across different levels of oxygen requirements and across VOC periods in a large US healthcare network on the outcome of 14- and 28-day mortality. Garibaldi 2021 (18,328 pairs of remdesivir users and non-users) 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 for the outcome of time to improvement and time to death.

Results

Mozaffari et al. 2023

In the LFO group, 4315 (6.4%) patients who received remdesivir and 5918 (8.8%) matched who did not receive remdesivir died within 14 days. By 28 days, 6641 (9.8%) from the remdesivir group and 8305 (12.3%) from the matched non-remdesivir group had died across VOC periods. The 14- and 28-day in-hospital mortality (adjusted hazard ratio [aHR]) among patients requiring LFO across VOC periods among the remdesivir group compared to the non-remdesivir group 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 (age, admission month, admission venue (ICU vs. general ward), and baseline concomitant COVID-19 treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab).

Among the HFO/NIV patients, 5853 (16.8%) patients who received remdesivir and 6770 (19.4%) who did not receive remdesivir died within 14 days. By 28 days, 9009 (25.8%) from the remdesivir group and 9853 (28.3%) from the non-remdesivir group had died. After adjustment for covariates, the 14- and 28-day in-hospital mortality adjusted hazard ratio (aHR) among patients requiring HGO/NIV across VOC periods in the remdesivir group compared to the non-remdesivir group was 0.83 (95% CI, 0.77 to 0.89) and 0.88 (95% CI, 0.82 to 0.93), respectively.

In the IMV/ECMO group, 1157 (27.8%) patients who received remdesivir and 1470 (35.3%) who did not receive remdesivir died within 14 days. By 28 days, 1724 (41.4%) from the remdesivir group and 2105 (50.6%) from the non-remdesivir group had died. After adjustment for covariates, the 14- and 28-day in-hospital mortality aHR among patients requiring IMV/ECMO across VOC periods in the remdesivir group compared to the non-remdesivir group 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% compared with 5.4% and 9.1%, respectively, for the non-remdesivir group. After adjusting for demographics and clinical characteristics, the odds ratio (OR) of 30-day COVID-19-related readmission and all-cause readmission among 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 patterns of OR of 30-day readmission in remdesivir-treated patients were observed across all variant time periods.

Finn et al., 2022

Remdesivir treatment was associated with a longer length of hospital stay with a 3.27-day average increase relative to non-remdesivir treated patients (95% CI, 2.11 to 4.44). This effect was most pronounced in patients with severe COVID-19 symptoms, where the increase in the length of stay 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 only a slight increase in their hospital stay.

Overall, patients treated with remdesivir had a 19% reduced risk of being readmitted to the hospital within 30 days, but the 95% CIs crossed the null (95% CI, 0.59 to 1.13). This reduction in readmission risk was pronounced in patients with mild COVID-19 symptoms, where they were 69% less likely to be readmitted if they received remdesivir with an RR of 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 with an HR of 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 LCS. Treatment with remdesivir led to a 35.9% reduction in LCS rate in follow-up.

At Visit 1, 123 vs. 81, patients were not affected by LCS in patients who received remdesivir compared to those who did not, respectively; 27 vs. 120 patients had a PCFS score of 2 to 3 in the remdesivir-treated patients compared to non-remdesivir treated, respectively; 13 vs. 85 patients with a PCFS score greater than 3 had a PCFS score of 2-3 in the remdesivir-treated patients compared to non- remdesivir treated, respectively. All differences in the two groups were statistically significant (P < 0.001).

Survival analysis was carried out comparing the patients treated with remdesivir and the non-remdesivir group according to the diagnosis of LCS in the follow-up with significant difference between the two groups ($\chi 2 = 14.614$, P < 0.001).

Kikuchi K et al. 2021

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

A total of 392 patients were analyzed; among them, 98 patients treated with remdesivir, matched with 298 patients not treated with remdesivir. The HR for OS was 0.45 (95% CI, 0.26 to 0.80) in the group treated with remdesivir and was considered higher than those not treated with remdesivir. The mean (SD) of the duration of hospitalization was 20.9 ± 13.2 days in the patient group who

were treated with remdesivir and 16.2 ± 8.1 days in the patient group who were not treated with remdesivir (difference = 4.7 days; 95% CI, 2.2 to 7.4).

Seethapathy R et al., 2022

Among patients who were not on dialysis prior to initiating remdesivir, one developed worsening kidney function (defined as ≥ 50% increase in creatinine or initiation of kidney replacement therapy and three in the historical control group.

There were no significant differences in adverse events 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 controls (P = 0.03). No significant differences were observed between the two groups in the lowest hemoglobin or peak ALT; only peak glucose was significantly different. In-hospital creatinine trajectories among remdesivir-treated patients, only one patient met predefined criteria for worsening kidney function due to initiation of KRT, and among the non-remdesivir-treated controls, three patients experienced a greater than 50% increase in serum creatinine.

Early discontinuation of remdesivir occurred among four patients (14%) due to safety concerns of elevated transaminase levels and low eGFR. The overall mortality rate during the hospital stay was 19% (n = 6) in the remdesivir-treated patients and 23% (n = 7) in non-remdesivir-treated controls (P = 0.71).

Seethapathy R et al., 2023

Mean peak creatinine was 2.3 mg/dL (95% CI, 1.98 to 2.57) and 2.5 mg/dL (95% CI, 2.13 to 2.89) 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 greater than or equal to 5 post-treatment creatinine measurements.

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

Among the remdesivir-treated patients 8 (4.6%) received kidney replacement therapy during their hospitalization compared to 11 (6.3%) from the matched untreated historical comparators.

A total of 120 surviving patients were measured, and the average eGFR at day 90 was 54.7 mL/min/1.73m^2 (SD = 20.0) in remdesivir-treated patients (N = 66) compared to 51.7 mL/min/1.73m^2 (SD = 19.5) among untreated historical comparators (N = 54).

Mozaffari et al., 2023

Unadjusted mortality rates were lower among remdesivir patients compared with non-remdesivir patients across all VOC periods and all levels of baseline supplemental oxygen requirement. Among the remdesivir group, 11.1% of patients died within day 14, and 17.7% died within day 28. In the non-remdesivir group, 15.4% of patients died within day 14, and 22.4% died within day 28. 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) and 0.75 (95% CI, 0.68 to 0.83) at 14 and 28 days, respectively. Similar results were seen during each VOC period and were most pronounced during the pre-Delta period at the 14-day assessment, with HR for pre-Delta, Delta, and Omicron were 0.59 (95% CI, 0.48 to 0.71); 0.77 (95% CI, 0.65 to 0.92); and 0.75 (95% CI, 0.63 to 0.90), respectively. At 28 days, HR for pre-Delta, Delta, and Omicron 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.

Regarding mortality rate among subgroups of patients with no supplemental oxygen charges in hospitals documented to charge for supplemental oxygen (NSOc) on admission within the remdesivir group, the HR 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 LFO on admission, HR 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 HFO/NIV or IMV/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%) from the remdesivir group and 12,510 (68.3%) from the non-remdesivir group achieved clinical improvement before 28 days with a median time to clinical improvement of 7 days (IQR = 5,19) in the remdesivir group and 9

days (IQR = 5,28) in the non-remdesivir group. The aHR for clinical improvement at 28 days in the remdesivir group was 1.19 (95% CI, 1.16 to 1.22). The aHR for clinical improvement among the remdesivir patients receiving no oxygen was 1.30 (CI, 1.22 to 1.38) with a median 5 days of (IQR = 4,13) for the remdesivir group compared to 7 days (IQR = 5 to 15) in controls.

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

There was no significant impact of remdesivir on mortality overall, with aHR of 1.02 (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 matched controls.

The aHR for mortality among the patients on room air 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 matched controls. The aHR among remdesivir patients on low-flow oxygen was 0.85 (95% CI, 0.77 to 0.92), and 28-day mortality of 8.4% (865 deaths) for remdesivir patients compared to 12.5% (1,334 deaths) for matched controls.

Among the remdesivir patients receiving HFNC or NIPPV, the aHR was 1.10 (95% CI, 1.01 to 1.20) and 28-day mortality of 28.6% (1,137 deaths) in the remdesivir group compared to 34.0% (1,237 deaths) in matched controls. While in the remdesivir patients receiving IMV, the aHR was 1.17 (95% CI, 1.04 to 1.32) and 28-day mortality of 46.7% (552 deaths) in the remdesivir group compared to 43.9% (686 deaths) for matched controls.

The aHR clinical improvement by Day 28 in the group who received remdesivir plus dexamethasone vs dexamethasone alone in the overall patient population was 1.21 (95% CI, 1.18 to 1.25). Similarly, for patients on room air and on low-flow oxygen, the aHR 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 vs dexamethasone alone in patients on low-flow oxygen was 0.83 (95% CI, 0.76 to 0.91).

Critical Appraisal

Guidance for Reporting Real-World Evidence forms the foundation for transparent reporting of RWE studies in Canada and facilitates appraisal of RWE by CADTH. All applicable sections in the Guidance should be reported when submitting RWE studies as part of a reimbursement review. Many RWE studies submitted as part of this review were missing important information. Information as to why a non-Canadian setting was chosen, 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, and how that 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, including variables that could not be captured and potential impact on study results were not provided.

The pivotal trial data lacks information regarding the effect of remdesivir on mortality in more recent variants of the COVID-19 virus. Mozaffari et al. 2023 is a large observational study that found that remdesivir reduced 14- and 28-day mortality compared with no remdesivir in patients hospitalized for COVID-19 between December 2020 and April 2022. Mozaffari et al. 2023 may address a gap in the pivotal trial data as 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 or vaccines administered prior to hospitalization. Although many comorbidities were controlled for, there remains a potential for imbalances in unmeasured confounders and residual confounding. Similarly, Mozaffari et al. 2024 is a large observational study that found that remdesivir reduced 30 day all-cause and COVID-19 related rehospitalization compared to no 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 the potential for missing data on the outcome of rehospitalization is not clear. There is also a lack of information about time since symptom onset, treatments received prior to hospitalization. There was a lack of matching. Despite inclusion of numerous variables in the multivariate regression, there is still a potential for unmeasured

confounders. For both Mozaffari et al. 2023 and Mozaffari et al. 2024, it is unclear whether the information from the US cohort is generalizable to Canada. Vaccine uptake and background disease risk as well as 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 on in hospital 14 and 28-day mortality compared with non-remdesivir treated patients and to extrapolate the effect to current practice in Canada.

The pivotal trial data lacks clear information about the effect of remdesivir on outcomes that occur post hospital discharge. Finn A et al. 2022 is a small observational study (742 remdesivir users matched to 1,539 non-users) that used EHR data from 3 hospitals in Rhode Island and found that remdesivir receipt reduced hospital readmission 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 Finn A 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 post-discharge 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 post hospital discharge for patients hospitalized with COVID-19 and to extrapolate the effect to current practice in Canada.

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

The pivotal trial data lacks clear information about the effect of remdesivir in patients with renal insufficiency. Three RWE studies were submitted to address this: Kikuchi K et al. 2021, Seethapathy R et al., 2021, and Seethapathy R et al., 2023. Kikuchi K et al. 2021 is a small observational study (98 remdesivir users were matched to 294 non-users) 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. Seethapathy R et al., 2021 is a small observational study (31 matched remdesivir users) that used EHR data from a single US hospital to examine the relationship between remdesivir in patients with eGFR less than 30 mL/min/1.73m^2 and adverse events from May 2020 and January, 2021 for remdesivir users and March and April 2020 for non-users. Finally, Seethapathy R et al., 2023 is a small observational study (175 matched remdesivir users) that used EHR data from a single US hospital to examine the relationship between remdesivir in patients with eGFR from 15 mL/min/1.73m2 to 60 mL/min/1.73m2 and adverse laboratory based renal outcomes from April 2020 and November 2020 for remdesivir users and March and April 2020 for non-users. However, Limitations to all 3 studies and the inability to extrapolate the effect to current practice in Canada preclude conclusions about the effect of remdesivir for patients admitted to hospital with COVID-19 and receiving dialysis or with reduced renal function.

The pivotal trial data lacks clear information about the effect of remdesivir in patients who are immunocompromised. Mozaffari et al. 2023 is a large observational study (14,169 matched remdesivir users) that used a US dataset and found that remdesivir reduced 14- and 28-day mortality in patients compared to non-users who were immunocompromised and hospitalized for COVID-19 between December 2020 and April 2022. Mozaffari et al. 2023 may address a gap in the pivotal trial data as it describes comparative effectiveness of remdesivir on the outcomes of 14- and 28-day mortality in immunocompromised patients. Limitations included lack of information about time of symptom onset, treatments or vaccines administered prior to 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 immunocompromised patients in Canada due to uncertainty about the generalizability of the US cohort to Canada.

Garibaldi 2021 was submitted by the sponsor to address the effect of remdesivir in patients receiving dexamethasone, and is a large (18,328 pairs of remdesivir users and non-users) 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. Garibaldi 2021 may address a gap in the pivotal trial data, however the analysis of remdesivir plus dexamethasone to 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 or discharged alive without worsening of the WHO severity score within 28 days), lack of information about time since symptom onset or treatments

received prior to hospitalization. Approximately half of the remdesivir patients were unable to be matched, a potential source of bias and 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 and background disease risk as well as 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 time to improvement compared with non-remdesivir treated patients 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, LYs
Time horizon	6 weeks
Key data sources	ACTT-1 trial Real world evidence (Mozaffari et al., 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 COVID-19, 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 which are 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 healthcare 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 to $4,208,181 per QALY gained compared to SoC. The incremental costs of remdesivir were similar in all CADTH's reanalyses (approximately $3,600), and the incremental QALYs ranged from 0.0014 to 0.0009. A price of $317 to $396 per 5-day treatment course (reduction of

Component	Description
	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; LY = life-year; QALY= quality-adjusted life-year; SoC = standard of care
Note: Dose regimen for pediatric patients is as follows: Pediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg): 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 COVID-19 patients 12 years and older (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 remdesivir's duration of treatment 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:

1 expert committee member did not attend.

Conflicts of interest:

None