CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

remdesivir (Veklury)

(**Gilead Sciences Canada, Inc.**)

Indication: Hospitalized patients ≥12 years of age (weighing at least 40 kg) with pneumonia requiring supplemental oxygen.

March 4, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Clinician Input

CADTH Project Number: SR0833-000

Generic Drug Name (Brand Name): Remdesivir (Veklury)

Indication: Adults with COVID-19 who newly require supplemental low-flow oxygen or increase in supplemental low-flow oxygen from baseline (primarily hospitalized patients)

Name of Clinician Group: Ontario Health Infectious Diseases Advisory Committee

Authors of Submission: Dr. Michaeline McGuinty, Sumit Raybardhan, Dr. Gerald Evans, Dr. Lucas Castellani

1. About Your Clinician Group

The Ontario Health Infectious Diseases Advisory Committee provides clinical guidance and advice to Ontario Health on infectious diseases issues such as evidence-informed advice on treatment strategies, recommendations on place in therapy for new or existing anti-infective therapies and advising on conservation strategies where anti-infectives are in short supply.

2. Information Gathering

The information was jointly discussed via email.

3. Current Treatments and Treatment Goals

Remdesivir is an antiviral that modifies the underlying COVID-19 mechanism by preventing viral replication.

Remdesivir is currently approved by Health Canada for the treatment of 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. The recommended treatment regimen is a 200 mg IV loading dose on Day 1, followed by 100 mg IV once daily on Day 2 and onwards. The duration for adults and pediatric patients (weighing at least 40 kg) is at least 5 days total and not more than 10 days, and up to a total of 10 days for pediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg).

Other drug treatments available in Canada for patients requiring supplemental oxygen therapy (primarily hospitalized patients) include the following immunomodulators, all of which help to treat the hyperactive inflammatory response to SARS-CoV-2 infection through varying mechanisms of action:

- Dexamethasone: Corticosteroid
- Baricitinib: Janus kinase inhibitor
- Tocilizumab: Anti-interleukin (IL)-6 receptor monoclonal antibody
- Sarilumab: Anti-IL-6 receptor receptor monoclonal antibody

Other non-drug treatments include the use of supplemental oxygen.

Treatment Goals:

- Reduce the severity of symptoms
- Prevent progression to critical COVID-19 disease (e.g. requirement for high-flow supplemental oxygen and/or vasopressor or inotropic support, ICU admission)
- Accelerate symptom recovery and viral clearance
- Prevent/reduce the need for new high-flow supplemental oxygen (e.g., Optiflow, AIRVO), non-invasive ventilation (NIV, e.g., BIPAP), mechanical ventilation (MV), or extracorporeal membrane oxygenation (ECMO)
- Reduce the duration of hospitalization

- Prevent long-term sequelae (e.g. post COVID-19 condition)
- Prevent death

4. Treatment Gaps (unmet needs)

4.1. Considering **the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.**

Not all patients respond to currently available treatments.

Limitations associated with remdesivir:

1. *Administration*: Remdesivir is only available as an IV formulation, so patients require IV access to receive remdesivir therapy. It cannot be easily self-administered by patients at home and generally requires administration by a nurse or other health care professional.

2. *Generalizability:* The landmark randomized controlled trials (RCTs) for remdesivir (e.g. ACTT-1, SOLIDARITY, and CATCO) were conducted before the emergence of the Omicron variant, widespread COVID-19 vaccination or immunity from previous COVID-19 infection. Consequently, the generalizability of their findings to the current population in Canada is unknown given the high degree of pre-existing immunity from vaccine or natural infection.

3. *Optimal Window for Initiation:* The optimal timing to initiate remdesivir from date of symptom onset is unclear. Data from the ACTT-1 study suggest a greater benefit when remdesivir is initiated within 10 days of symptom onset, although the data may be driven by the subgroup of patients who received remdesivir within 6 days of symptom onset. In the CATCO study, the median time from symptom onset to randomization was 8 days, whereas SOLIDARITY did not provide data on time from symptom onset to enrollment.

   The consensus from various jurisdictions is to administer remdesivir as early as possible in the time course of disease. The National Institutes of Health (NIH) suggest within 10 days of symptom onset. The World Health Organization (WHO), British Columbia Centre for Disease Control (BC CDC), Alberta and Ontario COVID-19 treatment guidelines do not outline a time limit in relation to symptoms or COVID-19 positive test date for remdesivir use in hospitalized patients with severe COVID-19. The Manitoba COVID-19 treatment guidelines comment that there is no time limit in relation to symptoms or test positive date for remdesivir use in hospitalized inpatients requiring new low-flow supplemental oxygen.

4. *Optimal Duration of Treatment*:

   The landmark RCTs for remdesivir (e.g. ACTT-1, SOLIDARITY, and CATCO) evaluated a 10-day duration of remdesivir with discontinuation at hospital discharge if it occurs before Day 10 of therapy. The Health Canada remdesivir monograph highlights a maximum duration of 10 days. Subsequent RCTs (e.g., GS-US-540-5773, GS-US-540-5774) demonstrated similar benefits in clinical status between 5- and 10-day courses of remdesivir. Five days has been widely adopted as the standard duration of treatment (e.g., NIH, BC CDC, Alberta, Ontario, Manitoba, New Brunswick) with discontinuation at hospital discharge if it occurs before Day 5 of therapy. In Feb 2024, Quebec updated its remdesivir clinical guidance document and recommended a 10-day treatment duration for patients hospitalized due to COVID-19. In the accompanying remdesivir rapid review, the subject matter experts from Quebec acknowledged that the current state of evidence suggests no difference between a 5- and 10-day course based on the GS-US-540-5773 and GS-US-540-5774 studies. However, they also highlighted their concerns that the GS-US-540-5773 trial was not being designed in a way to verify equivalence between a 5- and 10-day duration and the average methodological quality of the GS-US-540-5774 trial (e.g., open design).

   Uncertainty exists regarding the potential subset of patients who might benefit from a 10-day course of remdesivir. The NIH guidelines suggest clinicians may extend the treatment course to a total duration of 10 days in those who do not clinically improve, or those who have prolonged, symptomatic COVID-19 with evidence of ongoing viral replication (e.g., immunocompromised patients) since remdesivir acts by preventing viral replication. However, this practice is not consistent amongst clinicians and strong clinical evidence for extending the duration from 5 to 10 days for patients who are not clinically improving is lacking.

5. *Role in Combination Therapy*: The optimal role for remdesivir as part of combination is not well-defined.

   For hospitalized patients requiring high-flow nasal cannula (HFNC) or non-invasive ventilation, the NIH guidelines suggest adding remdesivir as combination therapy with two immunomodulators (e.g., dexamethasone and baricitinib) to enhance viral clearance in certain populations where active viral replication may persist (i.e., who are immunocompromised or have evidence of ongoing viral replication).

   Patients who are severely immunocompromised can have a unique COVID-19 trajectory with prolonged viral replication, despite the receipt of antiviral therapy. Different combination regimens have been studied in heterogeneous immunocompromised populations with varying clinical outcomes, making it challenging to draw definitive conclusions.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The CADTH remdesivir review is not expected to cause a shift in the current treatment paradigm. Remdesivir can be added to other immunomodulatory agents (e.g., corticosteroids, janus kinase inhibitor), which work on the hyperinflammatory pathway that tends to drive the disease course in the later stages of illness.

For hospitalized adults with COVID-19 who require low-flow supplemental oxygen, remdesivir would be used in combination with other treatments for patients.

- Dexamethasone is recommended as first-line treatment for hospitalized adults with COVID-19 requiring any supplemental oxygen because its use was associated with a mortality benefit.
- Remdesivir is recommended in addition to dexamethasone for adult patients hospitalized for COVID-19 who newly require low-flow oxygen supplementation or increased low-flow oxygen supplementation from baseline, without systemic inflammation (e.g., C-reactive protein ≥ 50 mg/L, ferritin ≥ 1000 µg/L) and do not have rapidly increasing oxygen needs (SOLIDARITY, ACTT-1).
- Some guidelines (e.g., BC CDC) recommend considering the addition of remdesivir to baricitinib for hospitalized adults with COVID-19 who are receiving high-flow oxygen or non-invasive ventilation and are deteriorating or not improving despite baricitinib. This is because combination therapy was shown to reduce time to recovery and accelerate improvement in clinical status compared to baricitinib alone (ACTT-2 study). However, a limitation of the ACTT-2 study is dexamethasone was not considered to be standard of care for hospitalized patients with COVID-19 at the time of patient enrollment and information is not available from a RCT to determine whether there would be similar benefits for remdesivir in combination with baricitinib in patients treated with dexamethasone.

In hospitalized adults with COVID-19 who required supplemental oxygen had at least one elevated inflammatory marker (CRP, D-dimer, LDH, or ferritin >ULN), remdesivir may be considered reserved for patients with a contraindication for baricitinib, because a mortality benefit was associated baricitinib compared to no baricitinib use in this population (COV-BARRIER), whereas no mortality benefit was found for remdesivir (SOLIDARITY, ACTT-1).

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Hospitalized patients who require supplemental low-flow oxygen are **best-suited** for treatment with remdesivir.

The landmark clinical trials that support remdesivir use in this group of patients include ACTT-1, SOLIDARITY, and CATCO. However, these trials were done before the emergence of the Delta and Omicron subvariants, as well as before widespread vaccination, so do not reflect the current Canadian context where most people have pre-existing immunity from vaccination and/or previous infection.

- **The ACTT-1** study compared a 10-day course of remdesivir to placebo and demonstrated a reduction in time to clinical recovery (10 days vs. 15 days), the benefit most apparent in those receiving supplemental oxygen and randomized during the first 10 days after symptom onset. There was no change in time to recovery for those requiring HFNC/NIV/MV/ECMO.

- **The CATCO** study compared a 10-day course of remdesivir to standard of care and did not find a decrease in hospital mortality but found patients who received remdesivir were less likely to require initiation of mechanical ventilation. The median time from symptom onset to randomization was 8 days.
- **The SOLIDARITY** study compared a 10-day course of remdesivir to standard of care and found a small but statistically significant reduction in mortality in patients receiving supplemental oxygen (who were not mechanically ventilated at baseline). In the same group, there was also a statistically significant reduction in progression to mechanical ventilation. This study did not include time from symptom onset to enrollment/initiation of remdesivir, nor did it describe which patients requiring supplemental oxygen required low-flow vs. high-flow oxygen.

The findings from the above landmark clinical trials have been corroborated by more recent real-world observational studies (e.g. Dobrowolska et al, Mozaffari et al), but the degree of benefit in the Omicron era is unknown in patients who have previously been vaccinated or infected with COVID-19.

> A retrospective study conducted in Poland by Dobrowolska et al. evaluated the clinical outcomes of hospitalized patients with COVID-19 during the Delta and Omicron variant waves who were treated with remdesivir (n=762) compared to a clinically-matched group not treated with any antiviral (n=1,060). Patients were categorized upon admission to hospital based on symptoms and baseline oxygen saturation (SpO_2) on room air (e.g., unstable symptomatic with SpO_2 91-95%, unstable symptomatic with $SpO_2 \leq 90\%$ and ARDS). No statistically significant difference for mortality by day 28 and requirement for mechanical ventilation for patients with the COVID-19 Omicron subvariant who received remdesivir compared to those who did not receive any antiviral treatment. In multiple logistic regression, remdesivir was found to be an independent predictor of lower mortality. Remdesivir administration within the first 5 days of symptom onset was associated with a statistically significantly lower need for oxygen therapy. The difference was not statistically significant when further stratified by age (>60 years or >80 years), but the subgroup analysis contained a small number of patient and may be underpowered to detect a difference. Limitations of this study include: the lack of data available on immunization status and history of previous COVID-19 infection.
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> A manufacturer-sponsored, retrospective study from the United States by Mozaffari et al. compared all-cause Day 14 and Day 28 inpatient mortality in hospitalized, immunocompromised patients who received remdesivir within the first 2 days of hospitalization to those who did not receive remdesivir across pre-Delta, Delta, and Omicron waves. The most common types of immunocompromised conditions among participants were the use of immunosuppressive medications (~40%) and moderate or severe primary immunodeficiencies (~30%). After adjusting for baseline and clinical covariates, remdesivir was found to be associated with significantly lower mortality, regardless of oxygen requirement and variant. Limitations of this study include: the lack of available data on treatment initiation relative to symptom onset or COVID-19 positive test, immunization status, and whether the patients had received any COVID-19 therapy prior to hospitalization.

The hospitalized patients requiring supplemental oxygen **least suitable** for treatment with remdesivir are those with critical COVID-19 who require high-flow supplemental oxygen support or mechanical ventilation. The SOLIDARITY trial did not show any mortality benefit in patients who required mechanical ventilation at baseline.

The patients best-suited for treatment with remdesivir would be identified based on a positive COVID-19 test via PCR, rapid molecular, or rapid antigen test (RAT). Clinician assessment of a patient's signs and symptoms would be required to determine COVID-19 severity.

Remdesivir should ideally be started early in the disease course when viral replication predominates. Any issues with access to testing in an individual who eventually clinically deteriorates to the point of requiring supplemental oxygen, could result in presentation to hospital outside of the optimal timeframe (less than 10 days) to initiate remdesivir.

Misdiagnosis is unlikely in clinical practice as a microbiologically-determined COVID diagnosis is commonly required prior to initiating remdesivir therapy. There may be circumstances where a prescriber may rely on patient-reported result of a COVID-19 test (e.g. RAT) that was obtained as an outpatient. However, if there was a concern about the reliability of patient-reported information, COVID-19 confirmatory testing is available in hospital.

Since information on the degree of oxygen requirement can be readily accessed for hospitalized, it is possible to identify those patients most likely to exhibit a response to remdesivir. At this time, there are no reliable risk prognostication models for remdesivir treatment response to predict which patients with specific comorbidities may derive the most benefit.

5.3. What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The 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, length of 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).

Some outcomes such as time to clinical improvement or the degree of clinical improvement may differ between studies. The definition of standard of care may also differ between studies.

Treatment response should be assessed until hospital discharge or death.

5.4. What **factors should be considered when deciding to discontinue treatment with the drug under review?**

If hospitalized patients on low-flow oxygen are started on remdesivir therapy, but progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed (NIH). However, it is unknown whether there is a benefit to completing the full course of remdesivir treatment.

The factors that should be considered when deciding to discontinue treatment with the drug include:

- **Disease progression**:

  Progression to critical COVID-19 (e.g., Requirement for HFNC, NIV, MV, ECMO, vasopressor/inotropic support) merits a reassessment of remdesivir therapy. This stage of illness is usually later in the disease course and driven by systemic inflammation/cytokine storm. For these patients, recommendations are mixed surrounding whether to continue or discontinue remdesivir therapy based on the unclear evidence of benefit and likelihood of minimal harm.

  For patients who progress to requiring HFNC/NIV:

  The benefit of remdesivir is not clearly established. As previously mentioned, the SOLIDARITY trial demonstrated a small and statistically significant reduction in mortality, and as a secondary endpoint, a reduction in progression to MV in patients requiring supplemental oxygen (who were not ventilated). The supplemental oxygen group contained both patients requiring low-flow oxygen and those requiring HFNC/NIV and these respective subgroups were not individually evaluated.

  The NIH similarly comment that remdesivir helps prevent progression to MV but does not clearly have established benefits in reducing recovery time or survival. The NIH recommend continuing remdesivir until the treatment course is complete. The BC CDC classify HFNC/NIV as critical COVID-19 and recommend discontinuing remdesivir in patients who progress to critical COVID-19 given its lack of benefit in improving survival or time to recovery.

  For patients who progress to requiring MV/ECMO:

  The NIH suggest continuing remdesivir until the treatment course is complete. The BC CDC recommend discontinuing remdesivir in patients who progress to critical COVID-19 given its lack of benefit in improving survival or time to recovery. The Manitoba COVID-19 treatment recommendations suggest discontinuing remdesivir if initiated for COVID-19 prior to intubation. The New Brunswick COVID-19 treatment guidelines do not recommend remdesivir for patients on HFNC, NIV, MV, or ECMO. However, for patients who progress to MV, they suggest daily reassessment of remdesivir and to consider discontinuation if the patient continues to deteriorate despite 48 hours of sustained MV.

- **Discontinuation of remdesivir due to adverse events**:

Remdesivir is known to cause elevations in alanine aminotransferase (ALT) which are usually mild, reversible, and self-limiting. However, it should be discontinued if ALT rises to greater than or equal to 5 times the upper limit of normal or if ALT elevations are accompanied by signs or symptoms of liver inflammation, increasing conjugated bilirubin, alkaline phosphatase, or INR.

Remdesivir should also be discontinued if the patient has signs and symptoms of a severe allergic reaction or other severe adverse drug reaction.

5.5. What **settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?**

The most appropriate setting for treatment with remdesivir is in a hospital.

A specialist would not normally be required to diagnose, treat, and monitor patients who receive remdesivir. However, in cases where off-label use of remdesivir is being considered (i.e., beyond the usual 5-day duration) due to specific circumstances (e.g., immunocompromised patients or where concerns of persistent viral replication exist), consideration should be given to involving an Infectious Disease specialist given the mixed evidence to support this practice.

6. Additional Information

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Michaeline McGuinty

Position: Clinician Scientist, The Ottawa Hospital

Date: 27-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this

clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Gilead	X			
Pfizer		X		
AstraZeneca	X			
GSK	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Sumit Raybardhan

Position: Pharmacy Practitioner, Infectious Diseases, North York General
Date: 27-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
N/A				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Gerald Evans

Position: Consultant, Infectious Diseases, Kingston Health Sciences Centre
Date: 28-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
N/A				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Lucas Castellani

Position: Infectious Diseases Physician; Medical Director Infection Prevention and Control, Sault Area Hospital
Date: 29-02-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
N/A				

* Place an X in the appropriate dollar range cells for each company.