CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

remdesivir (Veklury)

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

Indication: Non-hospitalized patients ≥12 years of age (weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

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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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Input

Name of Drug: remdesivir (Veklury®)

Indication: COVID-19 in non-hospitalized patients

Name of Patient Group: Gastrointestinal Society

Author of Submission: Jaymee Maaghop

1. About Your Patient Group

The GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to healthcare, and promoting gastrointestinal and liver health.

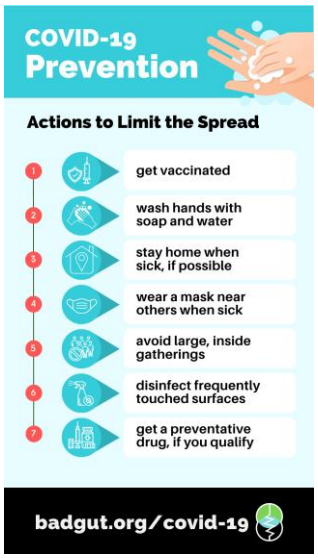
We are a national charity formed in 2008 on the groundwork of its partner organization, the Canadian Society of Intestinal Research (CSIR), which was founded in Vancouver in 1976. We receive national and international attention, simply because we have earned the respect of both the gastrointestinal medical community and Canadians who battle GI and liver issues daily. Our English and French websites received 9,329,479 pageviews in 2023.

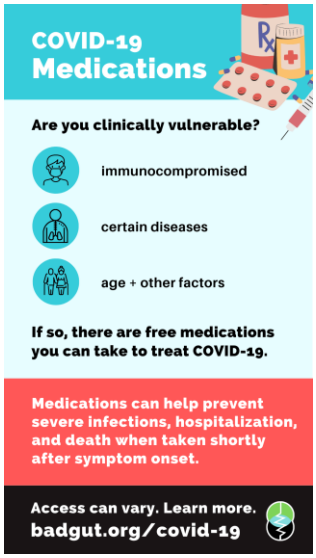
All our programs and services focus on providing Canadians with trusted, commercial-free, medically-sound information on gut (including obesity) and liver diseases and disorders in both official languages. Our BadGut® lectures, quarterly *Inside Tract*® newsletter, pamphlets, support groups, and educational videos arm Canadians with the information they require to better understand and manage their specific needs. We also work closely with healthcare professionals and governments at all levels toward system-wide improvements in care and treatment.

2. Information Gathering

The information we used to complete this submission was obtained primarily through meetings and discussions we have had with healthcare professionals, researchers, and academics, and first-hand experiences among staff who were affected by COVID-19.

We developed a COVID-19 Resource Hub, available in English (https://badgut.org/covid-19/) and French (https://badgut.org/covid-19-fr/?lang=fr), to support individuals across Canada affected by COVID-19 infections. It includes comprehensive information on prevention, testing, variants, treatments, nutrition, and how the virus affects the gut.





Since our focus as an organization is on gastrointestinal conditions, this submission will discuss the impacts of COVID-19 on the digestive tract.

3. Disease Experience

The COVID-19 global pandemic was triggered by the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV2). In Canada, the pandemic was declared in March 2020, leading to federal and provincial public health regulations aimed at limiting the spread of the virus. It has infected millions of Canadians, with more than 58,400 deaths so far.

The most common symptoms of COVID-19 are fever, tiredness, dry cough, difficulty breathing, aches and pains, nasal congestion, and a sore throat. They can also involve atypical symptoms, such as loss of smell or taste, or gastrointestinal (GI) symptoms such as nausea, vomiting, diarrhea, and abdominal pain. These can range from mild to severe. Children can also experience all these symptoms, with studies showing that they can affect up to a quarter of children infected with COVID-19.

Certain individuals are at increased risk of hospitalization or death from a COVID-19 infection. This includes people with a health condition that weakens their immune system (immunocompromised) and people who are considered clinically extremely vulnerable (CEV), such as those taking treatments for cancer, immunosuppressive treatment, high dose of steroids, and/or biologics (e.g., some medications for inflammatory bowel disease, primarily Crohn's disease and ulcerative colitis). Several conditions are also associated with CEV or high risk, such as being of advanced age, smoking tobacco, and having medical conditions such as obesity, diabetes, kidney disease, and alcohol use disorder.

The impact of COVID-19 on the digestive tract occurs in two primary ways. The first effect is that the virus attacks the body by interacting with the angiotensin converting enzyme 2 (ACE2) receptor, which is present in many organs and common on the cells that line our body surfaces, especially in the GI tract. When the virus binds to these receptors, it can cause damage and affect the intestinal lining, leading to diarrhea, stomach upset, vomiting, and inflammation. Severe cases may even lead to obstructions, co-infections, or intestinal necrosis and organ failure.

The other way COVID-19 affects the GI tract is by modifying the microbiome. Our gut microbiome is composed of trillions of bacteria and other microorganisms that help with metabolism, digestion, fighting infection, and mood regulation. Damage to the gut microbiome can lead to opportunistic infections, severe GI symptoms (pain, nausea, diarrhea), and even anxiety and depression.

Sadly, despite a history of infection with COVID-19, it is possible to contract the virus again. Several significant mutations to the virus continue to occur leading to variants of concern, so people reinfected with COVID-19 can experience similar or additional symptoms with the disease. There is little information and controlled research in this area, so we still do not fully understand the timeframe and other parameters of reinfection.

Although the World Health Organization declared the pandemic to be over on May 5, 2023, COVID-19 continues to mutate and create variants of concern, so the availability of effective vaccines and treatments remains paramount.

4. Experiences With Currently Available Treatments

There are a wide range of treatments available for COVID-19. Some are for prevention, including vaccines, while others focus on treating the infection. For this submission, we will focus on medications that treat a COVID-19 infection.

Cilgavimab and tixagevimab (Evusheld™) is indicated for the treatment of mild to moderate COVID-19 infection in those 12 years of age or older. It must be administered within 7 days of symptom onset to help reduce the risk for a severe infection. It is also the only medication currently approved for the prevention of COVID-19. It is administered as two intramuscular injections at the same time in separate locations of the body. It is approved for use in those who are immunocompromised and unlikely to mount an adequate response to COVID-19 vaccination or in those for whom COVID-19 vaccination is not medically recommended. While studies show that protection lasts at least 6 months after treatment administration, it is not expected to have significant protection against newer Omicron variants.

Bamlanivimab is only available for individuals who are at high risk of disease worsening. It is administered as a single intravenous (IV) infusion in a healthcare setting. Its use and availability vary by province and territory, with some jurisdictions advising against their use since its effectiveness against the virus is still being studied.

Casirivimab and imdevimab is a combination medication administered as a single IV infusion for the treatment of COVID-19 in people 12 years of age and older who are at high risk of being hospitalized or dying due to infection. However, similar to bamlanivimab, its use also varies by province and territory, with some jurisdictions advising against using it.

Sotrovimab (Xevudy®) is another IV medication available for people 12 years of age and older who are at high risk of hospitalization or death due to the infection. Similar to bamlanivimab and combination therapy casirivimab and imdevimab, Xevudy® is being assessed for its effectiveness and its availability varies across Canada.

Paxlovid™ is the only oral medication available in Canada and it is effective against Omicron variants. Unfortunately, it is challenging to access, especially in a timely manner, since it must be taken within 5 days of symptom onset. The administrative process required to access this treatment can be lengthy, and the criterion for eligibility varies by jurisdiction, with some enforcing stricter parameters for access.

Although it appears that individuals have a few options to protect them from severe COVID-19 infection or death, these treatments are difficult to access and may be limited in their effectiveness against the newer variants. Others require further research as provincial health regulators advise against their use, despite approval from Health Canada.

5. Improved Outcomes

Individuals who are at increased risk for severe COVID-19 need access to treatments that are effective against the newer variants. Since individuals who have a higher risk often live with an existing acute or chronic condition(s), they need a variety of treatments that do not present contraindications with their current medicines and therapies.

6. Experience With Drug Under Review

While we have not spoken with individuals who received remdesivir (Veklury®), we know that it is an effective option for patients who are in-hospital and for those who are at high risk of hospitalization or death due to COVID-19. This medication is also available for use in children and adults. It is administered by IV infusion in a healthcare setting, once daily for only three days.

Remdesivir is available as an effective option for individuals who have contraindications to nirmatrelvir/ritonavir (Paxlovid™). This is important as it provides patients with more treatment options to protect them from a severe COVID-19 infection. Paxlovid™ is also difficult to access, due to administrative barriers in some jurisdictions such as BC and is only effective when taken within five days of symptom onset.

Unfortunately, several provinces and territories do not have publicly available information on how to access remdesivir, and other provinces have stated that there is limited access to this treatment. We encourage CADTH to address these barriers in the implementation guidance.

7. Companion Diagnostic Test

Not applicable.

8. Anything Else?

n/a

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

No.

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

   No.

2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
n/a				

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

Name: Jaymee Maaghop
Position: Health Policy and Outreach Manager
Patient Group: Gastrointestinal Society
Date: 2024-03-04

Clinician Input

CADTH Project Number: SR0834-000

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

Indication: COVID-19 in non-hospitalized patients

Name of Clinician Group: BC Transplant Clinicians

Author of Submission: Catherine Cheung (Acting BC Transplant Pharmacy Manager)

1. About Your Clinician Group

BC Transplant (BCT) oversees all aspects of organ donation and transplant across British Columbia (BC) and manages the BC Organ Donor Registry.

Website: BC Transplant

Our consultation group consists of 7 members:

- Dr. Alissa Wright, MD (Transplant Infectious Disease Physician – Vancouver General Hospital, Vancouver, BC; member of BC COVID-19 Therapeutics Committee)
- Erin Waters, RN, MSc (Clinical Nurse Leader, Kidney Post-Transplant Clinic – St. Paul's Hospital, Vancouver, BC)
- Nilu Partovi, RPh, PharmD (Lung Transplant Clinical Pharmacy Specialist and Lower Mainland Pharmacy Services Director – Vancouver General Hospital, Vancouver, BC; member of BC COVID-19 Therapeutics Committee)
- Trana Hussaini, RPh, PharmD (Liver Transplant Clinical Pharmacy Specialist and Clinical Pharmacy Services Coordinator – Vancouver General Hospital, Vancouver, BC)
- Casara Hong, RPh, PharmD (Clinical Pharmacy Specialist, Kidney Post-Transplant Clinic – St. Paul's Hospital, Vancouver, BC)
- Catherine Cheung, RPh, PharmD (Acting Pharmacy Manager – BC Transplant, Vancouver, BC; member of COVID-19 Therapy Review and Advisory Working Group in BC)
- Eric Lun, PharmD (Executive Director – BC Transplant, Vancouver, BC)

2. Information Gathering

Since the beginning of the COVID-19 pandemic, there were a few research studies performed by several local solid organ transplant (SOT) clinician groups. BC Transplant is currently conducting a retrospective chart review on outpatient treatment of COVID-19 in heart/kidney transplant patients (in collaboration with the Heart Transplant Clinic at St. Paul's Hospital (Vancouver, BC) and the Fraser Health Post Transplant Clinic (Surrey, BC).

At BC Transplant, we formed a small consultation group with several key transplant clinicians (solid organ transplant ID physician, solid organ transplant pharmacists and nurses) who are involved in COVID-19 research/clinical practice in SOT patients. Information on their expert opinion and frontline experience of caring for solid organ transplant patients with COVID-19 were gathered during a recent consultation meeting.

3. Current Treatments and Treatment Goals

- As a province, BC currently recommend and have prioritized the use of remdesivir (over nirmatrelvir-ritonavir or NMV-r) in non-hospitalized (outpatient) SOT patients with mild to moderate COVID-19 symptoms, regardless of vaccine status or previous infection. SOT patients are severely immunocompromised individuals considered to be at the highest risk of progression to severe COVID-19 disease and part of the Clinically Extremely Vulnerable Group 1 (CEV-1) designation.
- The recommended dosing for remdesivir in this setting are as follows: 200mg IV on day 1, followed by 100mg IV on days 2 and 3 (200mg IV on day 1, followed by 100mg IV 48-72 hours later in eGFR <30ml/min) is recommended within 7 days of symptom onset as an alternative to nirmatrelvir/ritonavir. The full provincial BC CDC recommendations can be found here: Treatments (bccdc.ca)
- Although not studied extensively in SOT patients, these COVID-19 drugs (remdesivir and NMV-r) have been approved for use and recommended in practice guidelines for the outpatient treatment of transplant patients with mild to moderate COVID-19 symptoms.
- Goals of treatment include a reduction in COVID-related mortality, hospitalization or intensive care admissions in Solid Organ Transplant (SOT) patients.
- In BC, remdesivir remains a preferred COVID-19 treatment for transplant patients who:
    - are on tacrolimus/cyclosporine/sirolimus (due to significant drug-drug interaction with ritonavir/NMV-r; high risk for labile and unpredictable drug levels and toxicity)
    - have clinical factors which preclude NMV-r (e.g. graft rejection so immunosuppression cannot be held/stopped, decreasing/fluctuating eGFR therefore uncertain of renal dose adjustment for NMV-r)
    - unable to have timely or reliable follow up for adjustment of immunosuppression drug levels (i.e. unable to go for scheduled drug levels post-NMV-r treatment, live in remote geographic area precluding timely drug level reporting)

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.

- COVID-19 research studies amongst SOT patients are scarce and limited by heterogeneity in study design.
- At the beginning of the pandemic, there were no official COVID-19 treatments while unfortunately, transplant patients with infections in Canada had experienced high morbidity and mortality.
- COVID-19 treatment and vaccines were not well studied among SOT patients – long-term safety of these agents are not well-established and may have variable efficacy.
- New COVID-19 medication/treatment options that can improve convenience of administration are much needed.

5. Place in Therapy

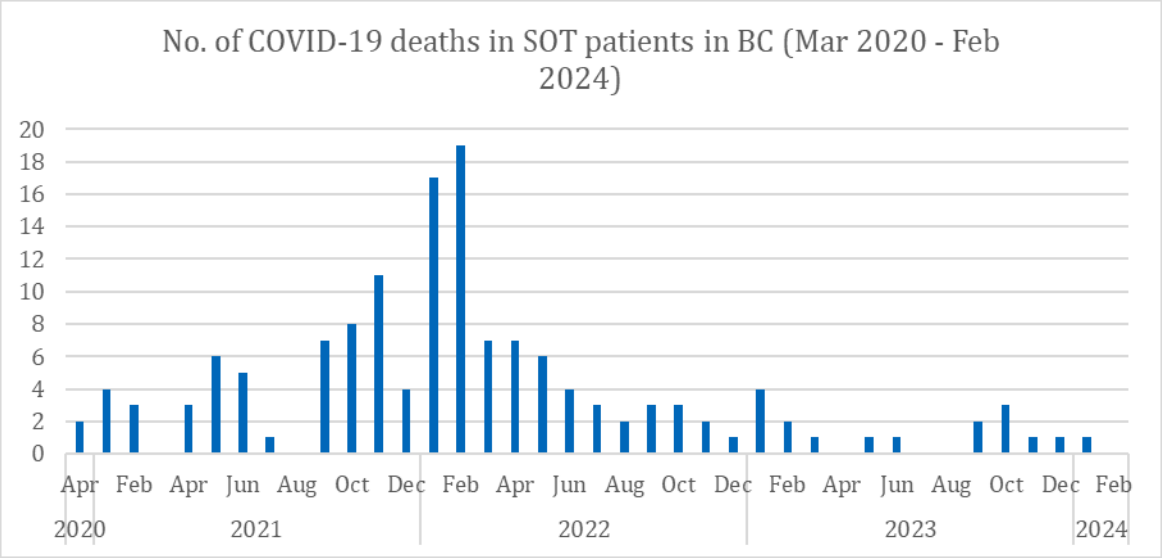
5.1. How would the drug under review fit into the current treatment paradigm?

Other drugs such as bamlanivimab, casirivimab-imdevimab, and bamlanivimab-etesevimab were previously approved as COVID-19 treatments. In particular, Sotrovimab was authorized by Health Canada on July 30, 2021 as a recombinant human monoclonal antibody that targets against the SARs-CoV-2. Unfortunately, all of these agents were later found ineffective against the newer COVID-19 variants such as the Omicron BA.2. Since April 2022, remdesivir has become the only intravenous COVID-19 treatment that could be effective against the newer subvariants. The active form of remdesivir acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase of coronaviruses including SARS-CoV-2.

Remdesivir is currently utilized as the main COVID-19 treatment in BC SOT patients, due to its better safety profile compared to NMV-r (in the context of significant drug interactions with commonly used immunosuppressant agents). There are only small case reports or series using NMV-r in SOT patients, making NMV-r a not well-established therapy in this population. The significant drug interaction between NMV-r and common immunosuppressants used to prevent transplant graft rejection (i.e. tacrolimus/cyclosporine/sirolimus) can result in potentially harmful and serious adverse events such as acute kidney injury due to supra-therapeutic immunosuppressant levels. Treatment modifications necessary to mitigate the impact of these significant drug-drug interactions often involves complex instructions that increases the risk of inadvertent errors by patients and caregivers.

Therefore, until there are better alternatives, continued access to remdesivir is essential for safe and effective treatment of COVID-19 infections in Solid Organ Transplant (SOT) patients because there are significant risks of not treating including potential patient hospitalization and mortality.

BC Transplant has been tracking COVID-19 related deaths among our SOT patients in BC (from March 2020 to Feb 28, 2024):[1]



The number of documented patient deaths in the year of 2020 may be underestimated due to inconsistent reporting from our BC transplant centres/clinics at the time.[1]

As of Feb 28, 2024, BCT estimated that 145 SOT patients in BC have lost their lives to COVID-19 (~2.4% of our approximately 6,000 SOT population).[1,2] Please note the SOT patient death rate was the highest during Jan/Feb 2022 (Omicron period) when access to COVID-19 outpatient therapies such as sotrovimab (recommended as first line therapy at the time) was very limited for transplant patients, especially for those living in some of the more remote areas. COVID-19 has been detrimental to our SOT patients, and it has continued to cause significant morbidity and mortality in this extremely vulnerable population despite herd immunity and high vaccination rate in the province.

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?

Unfortunately, it is still not entirely clear if remdesivir is the best COVID-19 therapy for SOT patients due to lack of large RCT or cohort studies in this population. In BC, all symptomatic SOT patients with mild to moderate COVID-19 symptoms who are within 7 days of disease onset would be recommended and eligible to receive remdesivir. Those who are asymptomatic or beyond the 7 days onset would be the least suitable to receive remdesivir. The rare SOT patient who is not on a calcineurin inhibitor (CNI) would be eligible for NMV-r and the least suitable to receive remdesivir.

As a reference, a few of our transplant groups in BC completed some research around the local use experience of COVID-19 therapies in SOT patients:

1. **Liver Transplant (VGH):** Our liver transplant group at Vancouver General Hospital reported 158 liver transplant patients had COVID-19 infection from March 2020 to September 2022. [3]

    - Three patients died within 30 days of COVID-19 infection (cause of death in 2 of these 3 patients was directly due to COVID-19). Twenty-four patients required admission to hospital, 7 requiring critical care support. 41 patients did not receive any COVID-19 therapy (for 26 patients there was none available at that time, 2 patients had contraindication to receive therapy due to a drug interaction, 1 patient had contraindication to receive therapy due to a medical condition, 1 patient refused, 10 patients reported their infection too late to the clinic to qualify).

    - Among the 112 outpatients, 92 patients (83%) received available antiviral COVID-19 treatment – 27 patients received Sotrovimab, 63 received remdesivir, 2 patients received NMV-r. Three patients were treated in hospital after initiating outpatient therapy, one with progression of COVID-19 illness despite starting remdesivir. Two patients had adverse effects of medications provided: one was prescribed NVM-r by a physician outside of the transplant program, which caused tacrolimus toxicity (serum concentration of 69.4 ng/mL) with nausea, vomiting, and diarrhea. Another patient had an episode of hypotension after receiving sotrovimab and sustained an acute kidney injury (AKI). Both patients fully recovered. There were no deaths on antiviral therapy.[3]

2. **Kidney Transplant (SPH):** Our kidney transplant group at St. Paul's Hospital reported 165 post-kidney transplant patients who tested positive for COVID-19 from Dec 2021 to April 2022 (the time Sotrovimab was available for outpatient treatment of mild-moderate COVID-19).[4]

    - Ninety-three patients received Sotrovimab and 72 patients received no treatment (39 patients were > 7 days post symptoms onset, 13 patients required oxygen at presentation, 7 patients declined treatment, 10 patients' treatment was declined by physician, 3 patients had logistical reasons to receive treatment). Patients who received sotrovimab and those that did not were compared in terms of demographics and baseline risk factors for progression to severe disease.

    - Multivariate logistic regression was used to analyze the association between the outcome variables (hospital admission, ICU admission and death) and treatment (sotrovimab vs. usual care). The odds of in-hospital mortality among renal post-transplant patients who acquired COVID-19 and received sotrovimab (intervention group) were statistically significantly lower than those in the control group, even after adjusting for risk factors known to contribute to the progression of severe disease (OR 0.16, 95% CI [0.03,0.89]). The odds of hospital admission was also significantly lower among those who received sotrovimab (OR 0.17, 95% CI [0.08, 0.39]). No statistically significant difference was seen for ICU admission (OR 0.32, 95% CI [0.09, 1.24]).[4]

3. **Heart Transplant (SPH) and Kidney Transplant (FH):** There is an ongoing retrospective chart review of COVID-19-positive heart and kidney transplant patients with mild to moderate symptoms who received sotrovimab, remdesivir, or NMV-r from St. Paul's Hospital and Fraser Health Post Transplant Clinic from March 2020 to July 2023 (collaboration between BC Transplant, Providence Health, and Fraser Health).[5] Preliminary results showed 110 heart transplant patients had COVID-19 during this period. Seventeen patients received sotrovimab, 46 patients received remdesivir, and 2 patients received NMV-r. Fifteen heart transplant patients (13.6% of cohort) have died during the study period, although it is unknown at this point whether these deaths were directly related to their COVID-19 infection.[5]

In summary, there is a general lack of RCT or cohort studies of robust quality to provide guidance to outpatient COVID-19 therapy in SOT patients with mild to moderate symptoms. However, SOT patients (who are chronically immunosuppressed) are considered at the highest risk for serious illness from COVID-19 infection and should be offered access to safe therapeutic options due to their extremely vulnerable status.

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?

When SOT patients receive outpatient remdesivir treatment, they're monitored by infusion clinic nurses daily (over the 3-day course) when receiving the drug, otherwise they are self-monitoring at home. However, patients are advised to go to Emergency for any worsening COVID-19 symptoms such as shortness of breath.

A clinically meaningful response to treatment would be a significant reduction in hospitalization, ICU admission, and death. These outcomes are similar to those studied in clinical COVID-19 research.

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

Remdesivir should be discontinued in case of any adverse events (e.g. increased serum creatinine, increased serum liver enzymes, hypersensitivity or infusion reaction), and SOT patients should be admitted to an acute care facility for any worsening symptoms despite therapy (increased shortness of breath and/or requiring supplemental oxygen or other supportive care).

5.5 What settings are appropriate for treatment with remdesivir? Is a specialist required to diagnose, treat, and monitor patients who might receive remdesivir?

SOT patients are usually closely followed by their transplant centres/clinics. Patients in BC have been told to contact their transplant centres/clinics if diagnosed with COVID-19 infection so they can be triaged in a timely manner for appropriate therapy. Transplant patients who received COVID-19 treatments are followed up by their respective transplant centres/clinics.

The other important consideration is to ensure remdesivir infusion is generally accessible – currently, regional health authorities around the province are providing this service.

6. Additional Information

Immunosuppressive medications such as tacrolimus, cyclosporine, and sirolimus have severe CYP3A4 drug interaction with ritonavir in NMV-r. Non-transplant physicians (e.g. family physicians and nurse practitioners) and other prescribers may be unfamiliar with such severe drug interaction leading to patient harm such as drug toxicity and potential transplant graft loss or death. We encourage CADTH to consider this aspect during the reimbursement assessment of remdesivir.

There was a BC cohort study using dispensing data of NMV-r from the Ministry, however SOT patients were not included (due to remdesivir instead of NMV-r being currently recommended for SOT patients in BC), and only the CEV 1 patients with hematological malignancies were enrolled. Compared with patients who were untreated, hospitalization and mortality after testing positive for COVID-19 was 9/280 (3.2%) vs. 2/280 (0.7%) if treated by NMV-r.[6] Similar studies in SOT patients in BC will be warranted.

Although SOT patients were prioritized for COVID-19 vaccines and subsequent booster/additional doses in BC since March 2021 (due to their CEV1 status), the efficacy of COVID-19 vaccines in this population is not well established. Transplant patients are known to get reduced response to COVID-19 vaccines due to their immunosuppressive state. Again, it is critical for SOT patients to continue having access to COVID-19 medication alternatives such as remdesivir. Although some evidence is available for NMV-r in non-transplant patients[6], BC Transplant encourages similar studies on the use of Remdesivir among SOT patients to ascertain its efficacy and safety in this CEV1 population.

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.

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

   No.

4. 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.

5. 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 <u>each clinician</u> 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: Dr. Alissa Wright

Position: Transplant Infectious Disease Physician – Vancouver General Hospital, Vancouver, BC

Date: 03-03-2024

☒ 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 - None declared

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

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

Declaration for Clinician 2

Name: Nilu Partovi

Position: Lung Transplant Clinical Pharmacy Specialist and Lower Mainland Pharmacy Services Director – Vancouver General Hospital, Vancouver, BC

Date: 03-03-2024

☒ 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 - None declared

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

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

Declaration for Clinician 3

Name: Trana Hussaini

Position: Liver Transplant Clinical Pharmacy Specialist and Clinical Pharmacy Services Coordinator – Vancouver General Hospital, Vancouver, BC

Date: 03-03-2024

☒ 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

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Paladin Labs Inc. Investigator Initiated Research Grant				X

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

Declaration for Clinician 4

Name: Erin Waters

Position: Clinical Nurse Leader, Kidney Post-Transplant Clinic – St. Paul's Hospital, Vancouver, BC

Date: 03-03-2024

☒ 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 4: Conflict of Interest Declaration for Clinician 4 - None declared

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

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

Declaration for Clinician 5

Name: Casara Hong

Position: Clinical Pharmacy Specialist, Kidney Post-Transplant Clinic – St. Paul's Hospital, Vancouver, BC

Date: 03-03-2024

☒ 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 5: Conflict of Interest Declaration for Clinician 5 - None declared

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

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

Declaration for Clinician 6

Name: Catherine Cheung

Position: Acting Pharmacy Manager – BC Transplant, Vancouver, BC

Date: 03-03-2024

☒ **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 6: Conflict of Interest Declaration for Clinician 6 - None declared

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

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

Declaration for Clinician 7

Name: Eric Lun

Position: Executive Director – BC Transplant, Vancouver, BC

Date: 03-03-2024

☒ 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 7: Conflict of Interest Declaration for Clinician 7 - None declared

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

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

8. References

1. BC Transplant (unpublished data). Obtained Feb 28, 2024.

2. BCT 2023 Statistics Infographic and Fact Sheet (transplant.bc.ca)

3. Reid J, Yoshida E, Hussaini T, Harrigan JA. A248 Outcomes of COVID-19 illness and access to appropriate treatment in liver transplant recipients in British Columbia throughout the pandemic. J Can Assoc Gastroenterol. 2023 Mar 7;6(Suppl 1):73–4. doi: 10.1093/jcag/gwac036.248. PMCID: PMC9991198.

4. Bateni B, Waters E, Bodman O. The efficacy of sotrovimab in preventing hospitalization and death in kidney post transplant patients with COVID-19: a single centre experience (unpublished manuscript).

5. Cheung C, Ma S, Chiu W, Alia T, Birks P, Toma M, Wright A. Clinical outcomes for COVID-19 positive transplant patients in BC – A retrospective chart review (unpublished data in an ongoing study). (UBC REB number: H23-02175)

6. Dormuth CR, Kim JD, Fisher A, Piszczek J, Kuo IF. Nirmatrelvir-Ritonavir and COVID-19 Mortality and Hospitalization Among Patients With Vulnerability to COVID-19 Complications. JAMA Netw Open. 2023;6(10):e2336678. doi:10.1001/jamanetworkopen.2023.36678

CADTH Project Number: SR0834-000

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

Indication: Adults with COVID-19 who do not newly require supplemental oxygen or increase in supplemental oxygen from baseline (primarily non-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

Current drug treatments available in Canada:

- Nirmatrelvir/ritonavir (Paxlovid)
- Remdesivir

Non-drug treatment

- Oxygen may be used for symptom management of patients with oxygen saturation less than 90-

92% Remdesivir and Paxlovid modify the underlying disease mechanism by preventing viral replication.

Treatment goals:

- Reduce the severity of symptoms
- Accelerate symptom recovery and viral clearance
- Prevent progression to severe COVID-19 disease (e.g., the need for new or increased supplemental oxygen)
- Prevent the need for emergency department visits
- Prevent 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 available treatments.

Limitations associated with current treatments:

1. Narrow time frame to initiate antiviral therapy (i.e., Remdesivir within 7 days, Paxlovid within 5 days) after COVID-19 symptom onset. Treatments with a longer window for initiation of therapy are needed to improve accessibility, convenience and to address key outcomes.
2. Since remdesivir is only available as an IV formulation and is administered via an infusion, an oral formulation of remdesivir or a longer-acting formulation of remdesivir (e.g., 1 dose = 3 day course) would improve convenience.

   Even though Paxlovid is available as an oral formulation, it has a high propensity for drug-drug interactions. Additional oral treatment options are needed to improve convenience as remdesivir is currently used as an alternative for patients who have a contraindication to Paxlovid.

5. Place in Therapy

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

Remdesivir is not added to Paxlovid as combination therapy for the treatment of mild to moderate COVID-19.

Paxlovid was approved for mild to moderate COVID-19 prior to remdesivir. Both treatments are approved to treat the underlying disease process.

Remdesivir is currently used as an alternative for patients with COVID-19 where Paxlovid cannot be given due to symptom duration outside the prescribing treatment window (i.e., Onset > 5 days but < 8 days) or where Paxlovid is contraindicated. Paxlovid contraindications are commonly due to drug-drug interactions (e.g., In solid organ transplant patients on calcineurin inhibitors or mammalian target of rapamycin inhibitors).

As of February 2024, most provinces' eligibility criteria for publicly funded remdesivir are based on the landmark randomized controlled PINETREE trial. A limitation of the PINETREE trial is that it was conducted in the pre-Omicron era and the participants were both unvaccinated against COVID-19 and had not been previously infected with COVID-19. If the eligibility criteria for reimbursement were to change, then it may cause a shift in the current treatment paradigm.

It may be reasonable to recommend patients try Paxlovid if the drug-drug interaction between the patient's medication(s) and Paxlovid can be safely managed. For most patients who have received a solid organ transplant, and for some patients on anti- arrhythmic medications or anti-epileptic medications, medication changes cannot be safely made and Paxlovid would be contra- indicated. This group has no alternative antiviral therapy for mild-moderate COVID-19 than remdesivir.

For patients who cannot swallow whole tablets, there is guidance that Paxlovid may be crushed and administered before initiating treatment with IV remdesivir.

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?

Patients most likely to respond to treatment:

1. Non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease, including patients presenting to the emergency department or residents of long-term care.
   OR
2. Hospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease, including nosocomial COVID-19 or patients admitted for reasons other than COVID-19 but have symptomatic mild to moderate COVID-19.

Patients most in need of an intervention:

Patients must be at high risk of hospitalization or death due to COVID-19, such as:

1. Age 65 and older

2. Immunocompromised patients:
- Advanced untreated human immunodeficiency virus (HIV) or treated HIV with a CD4 count equal or less than 200/mm^3
  or CD4 fraction equal or less than 15%
- Bone marrow transplant or stem cell transplant
- Solid organ transplant
- Active hematological malignancy
- CAR T-cell therapy in last 6 months
- Treatment for cancer (including solid tumors), limited to: systemic therapy in the last 6 months (e.g., chemotherapy, molecular therapy, immunotherapy, targeted therapies, monoclonal antibodies, excluding those receiving adjunctive hormonal therapy) or radiation therapy in the last 3 months
- Prednisone use equal to or greater than 20 mg/day (or corticosteroid equivalent) for 14 days or more, or other moderately or severely immunosuppressive therapies (e.g., anti-CD20 agents, alkylating agents)
- Primary immunodeficiencies
  - Hypogammaglobulinemia
  - Combined immune deficiencies affecting T-cells
  - Immune dysregulation such as familial hemophagocytic lymphohistiocytosis
  - Type 1 interferon defects caused by a genetic primary immunodeficiency disorder or secondary to anti-interferon autoantibodies
  - Diagnosed by an immunologist and requires ongoing immunoglobulin replacement therapy (IVIg or SCIg)
  - Primary immunodeficiency with a confirmed genetic cause (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)

3. Patients who have never received a COVID-19 vaccine or who have multiple co-morbidities such as:
- Active tuberculosis (treated or untreated)
- Cerebrovascular disease
- Chronic kidney disease, especially people receiving dialysis and those with CKD stage 4 or 5
- Chronic lung diseases, limited to: asthma, bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension
- Chronic liver diseases, limited to: cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis
- Cystic fibrosis
- Diabetes mellitus, type 1 or type 2
- Disabilities and developmental delay, including Down syndrome
- Heart conditions (e.g., heart failure, coronary artery disease, cardiomyopathies)
- Mental health conditions, limited to: mood disorders (including depression), schizophrenia spectrum disorders
- Neurologic conditions that cause an inability to control respiratory secretions or communicate disease progression (e.g., cognitive disorders such as Alzheimer-type dementia)

- Obesity (body mass index above 30 kg/m^2)
- Pregnancy or recent pregnancy (42 days post-partum/end of pregnancy)

The number of concurrent comorbidities and how well-controlled the chronic medical condition(s) are will affect the individual patient's risk for progression for severe COVID-19 disease.

4. Certain medical or social vulnerabilities may confer an increased risk of disease progression because affected individuals may experience challenges in recognizing, communicating or acting on progressive COVID-19 symptoms. Individuals at high risk include Indigenous people, Black people, other members of racialized communities; people experiencing intellectual, developmental, or cognitive disabilities; people who use substances regularly (e.g., alcohol); people who live with mental health conditions; and people who are underhoused.

How to identify patients best suited for treatment:

- Positive COVID-19 test (e.g., PCR, rapid molecular or rapid antigen test)
- Clinician assessment/examination/judgement of symptoms to determine COVID-19 disease

severity Issues related to diagnosis:

- Access to COVID-19 testing within 7 days of COVID-19 symptom onset
- No companion test required

Although COVID-19 symptoms may be similar to viral infections such as influenza, a microbiologically-determined COVID diagnosis is commonly required prior to initiating remdesivir therapy so the risk of misdiagnosis is low. However, there may be circumstances where a prescriber may rely on a patient-reported result of a COVID-19 test (e.g. RAT). If there was a concern about the reliability of patient-reported information, the prescriber may order or direct the patient for COVID-19 confirmatory testing, but that may delay the initiation of treatment for a drug that only has a 7-day initiation window from the time of symptom onset.

No validated prognostication tool for hospitalization or the progression to severe COVID exists based on different medical conditions. The degree of risk also varies depending on how well-controlled the medical condition is. Treatment decisions are often individualized based on the prescriber's assessment of patient risk based on factors such as age, immunocompromised status, vaccination status and the patient's comorbidities.

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?

Outcomes used in clinical practice are typically aligned to outcomes used in clinical trials. Clinical meaningful response to treatment includes the following;

- Resolution or improvement of symptoms (e.g., Headache, runny nose, sneezing, sore throat, fever, persistent cough, chills, dizziness, nausea, diarrhea, abdominal pain, joint or muscle pain, hoarse voice, new loss or altered sense of smell, chest pain, confusion/brain fog, delirium, irregular heartbeat, skin changes, shortness of breath, swollen glands, etc).
- No need for new or increase supplemental oxygen
- No emergency department visits
- No hospital admission
- No mortality

In terms of what defines a clinically meaningful improvement in frequency or severity of symptoms, this will vary amongst patients somewhat, and have some variation across physicians.

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

- Adverse effects from treatment such as ALT equal to or greater than 5 times the upper limit of normal.
- If new data find new COVID-19 variants are no longer susceptible to remdesivir.

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]?

Community setting (including nursing homes and long-term care), hospital outpatient clinic, hospital

emergency department A specialist is not required.

6. Additional Information

As of February 2024, the eligibility criteria for publicly funded remdesivir in many provinces are similar to Paxlovid. Key differences between the two antiviral options are the longer 7-day window after onset of COVID-19 symptoms for remdesivir initiation and a patient's ability to take oral medications. Consequently, remdesivir is commonly regarded as an alternative option to Paxlovid for the treatment of mild to moderate COVID-19, but is usually the only option for patients at very high risk (e.g., those with solid organ transplants).

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.

1.1 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

	Check appropriate dollar range*			
Company	**$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.

1.2 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

	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.

1.3 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.

1.4 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.