FAST FACTS

COVID-19 THERAPEUTICS IN TRANSPLANT PATIENTS

The Canadian **DONATION** and **TRANSPLANTATION** Research Program
Programme de recherche en **DON** et **TRANSPLANTATION** du Canada

Updated March 2023

The pace of change of COVID-19 has led to evolving prevention and treatment options for immunocompromised individuals, including transplant recipients. Changes in public health measures, along with emerging variants, means that transplant recipients remain vulnerable to COVID-19.

This fact sheet provides an overview of current treatments available to immunocompromised Canadian transplant recipients as of March 15, 2023. It is recommended you speak with your transplant team to determine what treatment option fits your circumstance. Note, not all treatment options outlined in this fact sheet are available in each province or territory. Please refer to Appendix I to learn more about the treatment options available in your region.

WHAT IS A COVID-19 VACCINE?

COVID-19 vaccines help prevent infection by helping a person produce antibodies against the SARS-CoV-2 virus. For immunocompromised and non-immunocompromised individuals, vaccines are the recommended option to prevent COVID-19.

All vaccines available in Canada are safe, effective, and have been approved by Health Canada. COVID-19 vaccines do not contain a live virus.

A list of COVID-19 vaccines available in Canada can be found here.

COVID-19 THERAPEUTICS FOR TRANSPLANT RECIPIENTS

Solid organ and hematopoietic stem cell transplant recipients have a higher risk of severe COVID-19 disease and risk of hospitalization, intensive care admission, and death than the general population [1,2] Due to reduced vaccine effectiveness caused by immunosuppressive medications, it is common for vaccinated transplant recipients to get COVID-19. [3,4,5,6,7,8] This is called a breakthrough infection.

Several treatments are authorized or under review by Health Canada to prevent severe COVID-19 disease in immunocompromised people, including transplant recipients. These treatments include anti-COVID-19 monoclonal antibodies and antiviral medications, given either for early treatment of mild-moderate disease or severe disease.

WORLD HEALTH ORGANIZATION (WHO) DEFINITIONS OF DISEASE SEVERITY FOR COVID-19:

Non-severe COVID-19: absence of any criteria for severe or critical COVID-19.

Severe COVID-19 – Defined by any of:
- oxygen saturation under 90% on room air;
- severe pneumonia;
- signs of severe respiratory distress. In adults, this includes accessory muscle use, inability to complete full sentences, and respiratory rate over 30 breaths per minute.

Critical COVID-19 – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

DISCUSSING TREATMENT OPTIONS WITH YOUR HEALTHCARE PROVIDERS

Early identification of COVID-19 infection is the first step to receiving timely treatment and reducing the likelihood of getting sick. When you receive a positive COVID-19 test, it is urgent you speak with your family doctor and/or transplant team because they will have your full medical history (i.e., your medications, allergies, other chronic illnesses) and will determine which treatment you qualify for. Treatments can be time sensitive, and their effectiveness may be reduced if you do not receive it within the recommended timeline. Furthermore, delays in treatment may increase your risk of experiencing severe symptoms.

What's in a name?

The World Health Organization (WHO) has a complex system for naming pharmaceutical substances, including antibodies. Names are built from "stems", groups of letters that compose the full name of the substance, based on its characteristics and origin.

PREFIX = random
SUBSTEM A = antibody target
SUBTEM B = species the antibody was "raised" or developed in
SUFFIX = defines characteristics of the antibody including specificity and engineered features

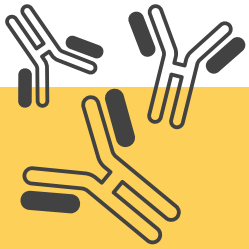
Example:
Sotrovimab

– sotr-o-vi-mab

- -o- = developed in mouse
- -vi- = targets a virus
- -mab = monoclonal antibody

For more details, see Appendix 1 of the Report on CDTRP National Forum: Emerging COVID-19 Issues in Transplantation. [9]

The generic antibody names given as above and the brand names of COVID-19 therapeutics are often used interchangeably. For example, your medical team may discuss the use of **tixagevimab/cilgavimab** as an option, instead of using the brand name, **Evusheld**. This fact sheet includes both the brand name and generic medical ingredient name so patients and their families are aware of all appropriate names you may encounter.



WHAT ARE MONOCLONAL ANTIBODIES?

Monoclonal antibodies are medicines that act like the natural antibodies our immune system produces to protect us from pathogens like harmful bacteria and viruses. Monoclonal antibodies are created by exposing a white blood cell to a virus, then isolating and mass-producing the antibodies that the white blood cell creates. [10] These antibodies are specific to the virus the white blood cell was exposed to, allowing the antibody to target the virus, and stop it from infecting other cells. Monoclonal antibodies were first generated as a therapy in 1975 [11] and have been used as targeted therapies to treat many conditions.

Monoclonal antibody therapies authorized for use in Canada to treat COVID-19 are bamlanivimab, sotrovimab, tocilizumab, (Actemra), tixagevimab/cilgavimab (Evusheld) and casirivimab/imdevimab. [12] Other monoclonal antibody treatments under review are regdanvimab (Regkirona) and bamlanivimab/estesivimab. [13]

Approved Monoclonal Antibody Therapies for Early COVID-19 Disease

Bamlanivimab | **Medical ingredient:** Bamlanivimab

Bamlanivimab is a monoclonal antibody authorized for use in Canada for adults and children over 12 years of age, weighing at least 40kg, with mild-moderate COVID-19 disease and/or at risk for severe COVID-19 illness and/or hospitalization. [14] The antibody binds to the SARS-CoV-2 spike protein and prevent the virus from infecting cells. In initial studies, patients who received bamlanivimab had reduced viral load, severity of symptoms, and hospitalization. Compared to placebo, the mean decrease in viral load from baseline was more than 99.97%. Only 1.6% of treated patients were hospitalized or visited the emergency department for COVID-19, compared to 6.3% of patients who received the placebo. [15]. One study specifically looking at bamlanivimab's effectiveness in transplant recipients (15 kidney, 2 liver, and 1 heart recipient) with mild-moderate COVID-19 disease found that treatment did not protect against hospitalization as strongly in this patient group as it did in the earlier study.

This treatment will be given on a one-time basis through an IV and it is recommended you received it within 10 days following the onset of clinical signs and symptoms of infection.

Detailed Product Monograph | **Summarizing Consumer Information**

Sotrovimab | **Medical ingredient:** Sotrovimab

Sotrovimab is a monoclonal antibody used to treat mild-moderate COVID-19 infection in adults and children over 12 years. [16] Sotrovimab was initially derived from a patient infected with SARS-CoV-1 in 2003. [17] Sotrovimab can inhibit SARS-CoV-2 infection and reduce severe disease. [18] During the Omicron wave, sotrovimab was studied in 51 adult solid organ transplant recipients, including kidney, liver, and heart recipients, with mild-moderate disease, and results indicated reduced rates of hospitalization and deaths. [19]

This treatment is administered through a one-time IV infusion and patients should be monitored during, and for at least one hour, after receiving the infusion. It is recommended patients receive this treatment as soon as possible after receiving a positive COVID-19 result. [16]

Sotrovimab remains an approved treatment for COVID-19. However, it is no longer in broad use in Canada, as laboratory tests indicate it may be less effective against current variants.

Detailed Product Monograph | Summarizing Consumer Information

Evusheld | **Medical ingredients:** Tixagevimab and cilgavimab

Evusheld is a monoclonal antibody therapy used for the prevention of COVID-19 and given to you as two intramuscular injections. It is recommended that Evusheld be used before being exposed to the virus as a preventative medicine, or after infection for treatment of mild to moderate COVID-19 disease. [20] The two antibodies, tixagevimab and cilgavimab, target the SARS-CoV-2 spike protein, the part of the virus that is needed to infect human cells. [21]

Evusheld is approved for use in adults and children over the age of 12 years old, weighing at least 40 kg, who are immunocompromised. [20] Evusheld can provide protection against severe COVID-19, in the general population and immunocompromised people [22,23] A higher dose, 600 mg, is more effective at neutralizing Omicron variants. [24,25,26] Research specifically in transplant recipients shows that those who receive a 600 mg dose are less likely to get COVID-19. [27] Learn more about Evusheld and transplant recipients here.

Evusheld is provided via two injections one after another and should be given as soon as possible after a positive COVID-19 test and within 7 days after the onset of symptoms. [20]

Evusheld remains an approved therapy in Canada. [28] However, recent evidence suggests Evusheld may not be effective for emerging COVID-19 variants and provinces are no longer recommending its use (See Appendix I).

Detailed Product Monograph | Summarizing Consumer Information

Casirivimab and Imdevimab | **Medical ingredients:** Casirivimab and imdevimab

Casirivimab and imdevimab is a combination monoclonal antibody medication that is approved to treat mild-moderate COVID-19 disease in adults and adolescents age 12 years or older, and weighing at least 40kg. Casirivimab/imdevimab is recommended for immunosuppressed people including stem cell and solid organ transplant recipients to help prevent worsening COVID-19 symptoms and is given after infection.

In patients that had no previous immunity to COVID-19, treatment with casirivimab/imdevimab decreased the likelihood of death. However, in patients who had previously developed an immune response, for example, from a prior infection, treatment with casirivimab/imdevimab did not change the likelihood of death. [29] Research suggests that casirivimab/imdevimab may reduce rates of severe disease progression, and hospitalization in transplant recipients. [30]

This treatment is given as a one-time infusion into a vein and on an emergency/temporary use to individuals who have mild-to-moderate symptoms for no more than 10 days and are not hospitalized.

Detailed Product Monograph | **Summarizing Consumer Information**

Monoclonal Antibody Therapies for Early COVID-19 Disease Under Review by Health Canada

Regkirona | **Medical ingredient:** Regdanvimab

Regdanvimab is a monoclonal antibody that binds to the spike protein of COVID-19.31 It is currently being evaluated in a Phase 2/3 study to effect its safety, tolerability and efficacy for treatment of mild-moderate COVID-19, in those who are at risk for severe disease, and do not need supplemental oxygenation. [32]

Detailed Product Monograph (Australia)

Bamlanivimab/etesevimab

Recent studies have found that bamlanivimab is more effective when combined with a second antibody, etesevimab. [33] As of March 24, 2023, bamlanivimab/etesivimab isunder review by Health Canada. In the United States, bamlanivimab and etesevimab are not currently authorized due to high frequency of the Omicron variant, for which this therapy cannot be used for treatment or post-exposure prevention. [34]

Treatment Fact Sheets

Approved Monoclonal Antibody Therapy for Severe COVID-19 Disease

Actemra | **Medical ingredient:** Tocilizumab

Actemra is monoclonal antibody used to reduce the need for mechanical ventilation and the likelihood of death. Actemra blocks an inflammatory receptor, which can decrease inflammation during severe disease progression. Actemra is recommended for use in individuals infected with COVID-19 presenting with moderate or critical disease. In the EMPACTA study, patients with COVID-19 pneumonia who received Actemra had less need for mechanical ventilation or death at day 28 by 7.3% compared to the placebo. However, patients treated with this drug did not have an improvement in survival. [35] In a study of 80 kidney transplant recipients with severe COVID-19, the drug decreased inflammatory markers in the blood, which correlated with better survival. [36]

This treatment is available as an intravenous infusion or injection and is used to treat hospitalized with COVID-19, who are receiving systemic corticosteroids, and require oxygen support. [37]

Detailed Product Monograph | Summarizing Consumer Information

WHAT IS AN ANTIVIRAL?

Antivirals are medications that are used to treat COVID-19 infections by preventing the virus from multiplying and infecting healthy cells and causing severe disease. [38] Antiviral medications can be used as treatments and as preventative measures. [39] Similar to monoclonal antibodies, antivirals have been used as targeted therapies since the 1960s. [40] Currently, Health Canada has approved the antivirals nirmatrelvir/ritonavir (Paxlovid) and remdesivir (Veklury) for use in Canada, while other antivirals such as baricitinib (Olumiant) and molnupiravir (Lagevrio) are under review. [13]

Approved Antiviral Therapies for COVID-19 Disease

Paxlovid | **Medical ingredients:** Nirmatrelvir/ritonavir

Paxlovid is an antiviral medication used for the treatment of mild-moderate COVID-19 infection in adults and children at high risk for severe outcomes. [41] The medication is composed of two different active agents, nirmatrelvir and ritonavir, which work to stop the virus from replicating. [42,43]

A high level of caution is needed for transplant recipients being treated with Paxlovid due to drug-drug interactions with anti-rejection medications. For example, the immunosuppressive medication tacrolimus is broken down in the body by an enzyme that Paxlovid inhibits. Therefore, taking Paxlovid can lead to tacrolimus levels increasing to high, resulting in potentially dangerous adverse events. Transplant recipients may still be prescribed Paxlovid, with careful management of their immunosuppression. [44,45]

Paxlovid is given as two tablets and requires a prescription from your healthcare team to ensure the doses meet your needs. It is recommended you receive Paxlovid within 5 days of symptom onset, and as soon as possible after a positive COVID-19 test. [41]

Detailed Product Monograph | Summarizing Consumer Information

Velkury | **Medical ingredient:** Remdesivir

Remdesivir is an antiviral active against SARS-CoV-1 and Middle East Respiratory Syndrome (MERS-CoV). [46] Remdesivir inhibits SARS-CoV-2 by stalling the virus' process of replicating itself. [47] It is provided to hospitalized adults and children over 12 with pneumonia and require extra oxygen to breathe and non-hospitalized adults with COVID-19 infection at high risk of severe illness. [48]

In the ACTT-1 trial (adaptive, randomized, double blinded, placebo-controlled design), patients with severe disease who were on remdesivir were more likely to show improvement at day 15, and had an 3.8% increase in survival. Patients given remdesivir had a quicker average recovery time of 10 days, compared to 15 days in the placebo group. [49] In small studies with kidney transplant recipients, remdesivir has been shown to be safe and effective at preventing death and hospitalization [50,51], and delayed the development of severe COVID-19-pneumonia in kidney transplant recipients. [52]

Remdesivir is given as an infusion over several days, determined by the severity of your illness. If you are not hospitalized, it is recommended you receive remdesivir within 7 days of showing symptoms. You will be given treatment every day for 3 days. If you are hospitalized, you may be given remdesivir every day for at least 5 days. [48]

Detailed Product Monograph | Summarizing Consumer Information

Antiviral Therapies Under Review for COVID-19 Disease

Lagevrio | **Medical ingredient:** Molnupiravir

Molnupiravir is an antiviral therapy active against the SARS-CoV-2 virus. Molnupiravir disrupts the virus' genetic sequences to disable replication. [53] In the MOVe-OUT study, risk of hospitalization or death at day 29 of infection was 6.8% lower compared to the placebo in unvaccinated adults with high risk of severe outcomes. [53]

Product Monograph (USA)

Olumiant | **Medical ingredient:** Baricitinib

Baricitinib was previously approved by Health Canada for rheumatoid arthritis [13] and works by reducing inflammation within the body. [54] Baricitinib is currently under review from Health Canada for the use in adults hospitalized with COVID-19 to reduce inflammation in severe disease.

Product Monograph

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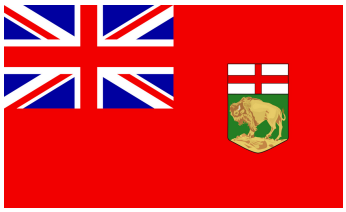
APPENDIX I

COVID-19 TREATMENTS PROVINCIAL QUICK LINKS

Alberta

British Columbia

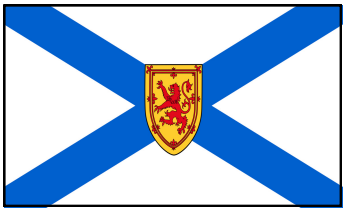


Manitoba

New Brunswick

Newfoundland and Labrador

Northwest Territories



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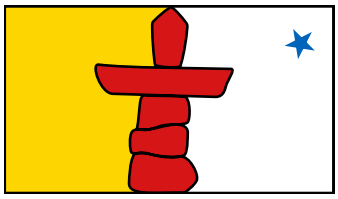
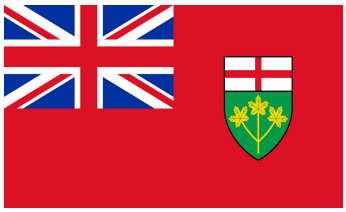
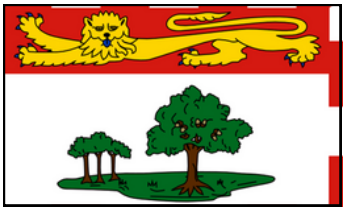


Nunavut

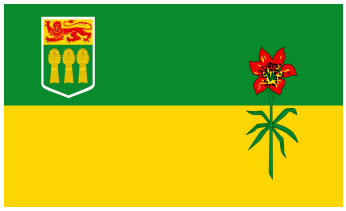


Ontario



Prince Edward Island

Québec



Saskatchewan

Yukon

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