FAST FACTS

TIXAGEVIMAB/CILGAVIMAB (EVUSHELD) AND TRANSPLANT RECIPIENTS:
CURRENT RESEARCH AND PROVINCIAL GUIDELINES

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

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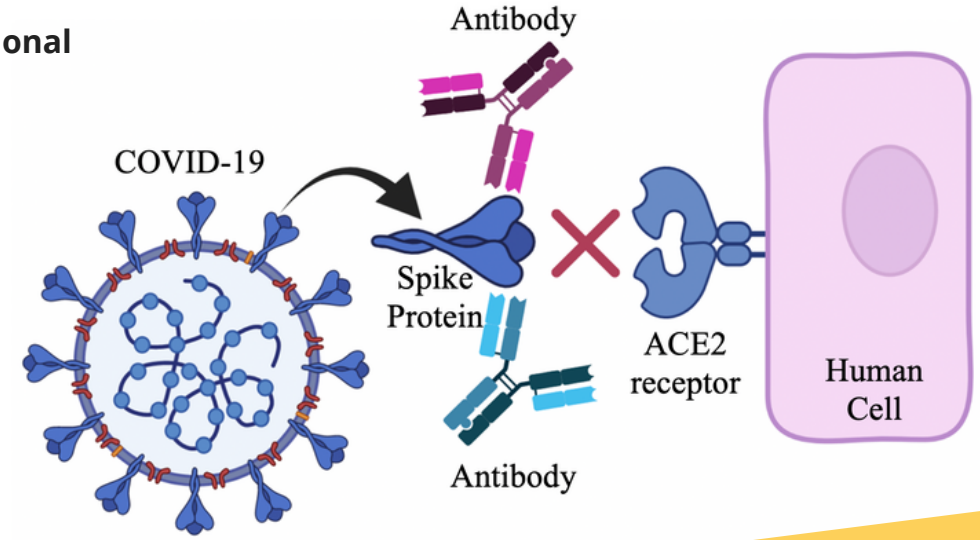
WHAT ARE MONOCLONAL ANTIBODIES AND HOW CAN THEY BE USED AS MEDICINES?

Monoclonal antibodies are synthesized proteins that act like the natural antibodies produced by our immune system. They can be used as medicines by supporting the immune system's ability to attack harmful cells or pathogens such as cancer, bacteria, and viruses. [1 ,2]

WHAT IS TIXAGEVIMAB/CILGAVIMAB (EVUSHELD) AND HOW DOES IT WORK?

Current studies have shown that transplant recipients develop poor immunity against COVID-19 despite multiple vaccinations compared to the general population. [3-8] For additional protection against COVID-19, tixagevimab/cilgavimab (brand name Evusheld) is a monoclonal antibody therapy approved for use in Canada. It can be used before being exposed to the virus as a preventative medicine, or after mild to moderate COVID-19 infection for the treatment of disease. [9] The two antibodies that compose Evusheld (tixagevimab and cilgavimab) target the SARS-CoV-2 spike protein, part of the virus that is needed to infect human cells. Tixagevimab and cilgavimab bind to two different locations on the spike protein, overlapping on a key part of the protein that the virus needs to bind human cells . When tixagevimab and cilgavimab bind to the virus, the virus cannot bind to human cells, therefore preventing the virus from causing an infection and COVID-19 disease. [10] Evusheld is approved by Health Canada for use in adults and children over the age of 12 years old, weighing at least 40 kg, who are immunocompromised. [9]

Combination Monoclonal Antibody Therapy
(multiple antibodies)



WHAT IS THE EVIDENCE THAT EVUSHELD CAN PREVENT AND TREAT COVID-19?

The PROVENT trial, published in June 2022, [11] assessed whether Evusheld can prevent symptomatic COVID-19 in adults who are at higher risk of exposure, higher risk of severe disease, or both. This randomized control trial analyzed 3810 patients who were likely to have an inadequate response to COVID-19 vaccination, of whom 172 were receiving immunosuppressive medications. In immunosuppressed patients, Evusheld reduced the risk of getting COVID-19 by 83.4% six months after receiving it. Those who got COVID-19 during the trial were infected with alpha, beta, and delta variants.

The TACKLE trial, published in Oct 2022, [12] evaluated whether Evusheld is effective as an early treatment for COVID-19 in unvaccinated adults with mild-moderate disease. The study used a randomized control trial design with 910 participants, most of whom had health conditions that increased the risk of severe outcomes of COVID-19, including 45 immunocompromised patients. There was no specific analysis of the efficacy or safety of the treatment in immunocompromised patients. Only 4% of participants who received Evusheld had outcomes such as severe COVID-19 or death, compared to 9% of participants in the placebo group. That is, participants who received Evusheld had about half the risk of severe disease or death than those receiving the placebo. The variants infecting patients in the study were B.1.1.7 alpha (most common), gamma, delta, lambda, mu, and beta.

PROVENT Trial

3810
TOTAL PATIENTS STUDIED

172
IMMUNUSUPPRESSED PATIENTS

↓ 83%
REDUCED RISK OF INFECTION FOR IMMUNOSUPPRESSED PATIENTS

TACKLE Trial

910
TOTAL PATIENTS STUDIED

45
IMMUNOCOMPROMISED PATIENTS

↓ 51%
REDUCED RISK OF SEVERE DISEASE OR DEATH FOR ALL PATIENTS

AGAINST WHICH VARIANTS IS EVUSHELD EFFECTIVE? HOW DO WE KNOW?

Researchers use a process called antibody neutralization to determine if antibody-based therapies are effective on new variants. Antibody neutralization is the process where an antibody binds to a protein on a virus, and inhibits the virus from infecting a cell, replicating, and causing disease. Different antibodies bind and block infection in different ways. [13]

Researchers can analyze antibody neutralization in laboratory experiments. To determine if antibodies can neutralize different variants of the virus causing COVID-19, scientists mix the antibody therapy, human cells, and virus-like proteins that resemble the different versions of the SARS-CoV-2 spike protein found in circulating variants. They then determine if the antibody can successfully inhibit the human cells from becoming infected.

Neutralization tests in the laboratory have shown that both tixagevimab and cilgavimab are less effective at neutralizing Omicron BA.1, BA.1.1, BA.2.75, BA.4/BA.5, and BA.4.6 variants. Tixagevimab is less effective with BA.2, BA.2.12.1, and BA.3, but cilgavimab remains effective for these variants. [14] The combination of tixagevimab/cilgavimab is much less effective for BA.2.75.2 and BQ1.1. [22]

Although reduced neutralization of new variants is being observed in the laboratory, it is not clear how well these findings represent what happens in the real world, when an antibody encounters the virus in an immunocompromised person. To test how well antibody therapies really work, researchers can test neutralization in animal models such as mice and use real-world evidence from patients.

In a study using mice as an animal model, Evusheld was still effective at reducing infection in the lungs with BA.1, BA.1.1 and BA.2. [15] In humans, studies have also found lower rates of infection and severe illness in immunocompromised people who were given Evusheld when Omicron variants were dominant. [16,17]

Dose also makes a difference in how effective an antibody therapy is against different variants. Current findings suggest that a 300 mg dose of Evusheld is less effective at neutralizing Omicron than earlier variants. [14,18,19] Researchers have analyzed the difference between the initial 300 mg dose and an increased 600 mg dose of Evusheld in real-world studies, hoping to see good protection against COVID-19 with a higher dose to compensate for the antibody neutralizing some new variants less well. One recent study found that vaccinated transplant recipients who received the higher dose of 600 mg had fewer breakthrough infections than those who received the 300 mg dose. [20]

In summary, current research suggests that Evusheld can provide protection against severe COVID-19 for some variants, in the general population and immunocompromised people. However, there is still a risk of breakthrough infection. The level of protection this drug provides against emerging variants is not well understood and depends on the dose given.

IS EVUSHELD USED IN CHILDREN?

Evusheld is authorized by Health Canada for use in children over 12 years of age weighing at least 40 kg, based on predictions of how the medication is processed by the body. No published research to date has assessed Evusheld safety and efficacy in children or adolescents under the age of 18 years old.

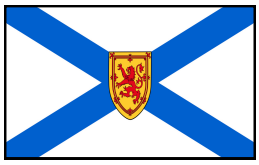
DOES EVUSHELD CAUSE HARMFUL CARDIOVASCULAR EFFECTS?

In the PROVENT clinical trial, cardiac events such as myocardial infarction and cardiac failure were reported in 0.7% and 0.3% of those who received Evusheld vs placebo, respectively. Some provinces have taken this risk into consideration in their eligibility guidelines, excluding people, for example, with a history of cardiovascular disease. A new study suggests there is no additional cardiovascular risk. [21]

EVUSHELD ELIGIBILITY CRITERIA FOR TRANSPLANT RECIPIENTS
AS OF JANUARY 11, 2023

The following is a high-level summary of publicly availably provincial eligibility guidelines relative to transplant recipients, which are subject to change.

For provincial updates, each link provided below has a publication date with when the information was last updated.



NOVA SCOTIA

Evusheld may be considered for severely immunocompromised individuals 12 years of age or older, with no known cardiovascular disease, and most recent COVID-19 vaccine being administered more than 14 days prior.

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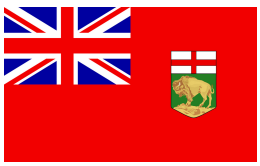

MANITOBA

Evusheld is available in limited supply in Manitoba as a pre-exposure prophylaxis treatment, for severely immunocompromised individuals over 12 years of age. Individuals must not have known cardiovascular disease.

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NEW BRUNSWICK

Evusheld is available for severely immunocompromised individuals 18 years of age or older, regardless of vaccination status. It is not recommended for those with a history of cardiovascular disease.

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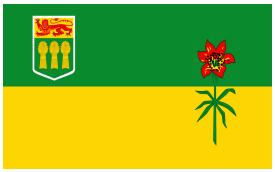

SASKATCHEWAN

Evusheld is available in Saskatchewan on a case-by-case basis. Those eligible are severely immunocompromised and who have additional risk factors that correlate with an extremely high risk of poor outcomes from COVID-19 and who do not have cardiovascular disease. Vaccinated individuals are eligible if their most recent COVID-19 vaccine was administered more than 14 days prior.

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QUÉBEC

As of December 2022, Evusheld is no longer being offered to any patients, based on the current Omicron subvariants circulating in Quebec (BQ.1, BQ1.1, BF.7)

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BRITISH COLUMBIA

Currently, Evusheld is not being recommended for use in British Columbia, even for those who are severely immunocompromised. In November 2022, the BC COVID Therapeutics Committee updated the guidance on Evusheld to reflect the prevalence of circulating variants of concern in BC (refer to "*Which variants is Evusheld effective against?*" section above).

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Provincial and territorial governments in **Newfoundland and Labrador, Prince Edward Island, Yukon, Northwest Territories**, and **Nunavut** have not released guidance or eligibility for the use of Evusheld as of January 2023.

ONTARIO

As of December 2022, Ontario is not recommending Evusheld for prevention or treatment for any patients. This is due to the prevalence of new COVID-19 variants (BA 4.6, BF.7, BQ.1 and BQ.1.1). See the "Which variants is Evusheld effective against?" section above.

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ALBERTA

Transplant recipients eligible for Evusheld are limited to specific sub-groups over 12 years of age and have received their most recent COVID vaccine more than 14 days prior. These include lung recipients, those receiving B cell or T cell depleting therapies or belatecept within the past 6 months, solid organ transplant recipients within six months post-transplant, and transplant recipients who are 60 years or older. Stem cell recipients or those who received chimeric antigen receptor T-cell therapy (CAR-T) therapy within the past twelve months are also eligible.

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REFERENCES

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[13]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1991280/#:~:text=Antibody%20neutralization%20is%20defined%20as,in%20the%20viral%20infection%20cycle

[14] https://www.fda.gov/media/154701/download

[15] https://www.biorxiv.org/content/10.1101/2022.03.17.484787v1

[16] https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciac625/6651663

[17] https://pubmed.ncbi.nlm.nih.gov/35926762/

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[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9126611/

[20] https://onlinelibrary.wiley.com/doi/10.1111/ajt.17128

[21] https://doi.org/10.1093/cid/ciac894

[22] https://doi.org/10.1016/S1473-3099(22)00733-2

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