Information about Evusheld (Tixagevimab and Cilgavimab)

Reference for health care providers who may be prescribing or administering Evusheld

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The information in this document was developed based on best available evidence and expert consensus as of the date of publication. There are limitations to the evidence that is currently available. Information about Evusheld, including its effectiveness against different variants of COVID-19, is evolving rapidly. Prescribers must determine whether adopting suggested information is clinically appropriate for individual patients through a risk-benefit assessment.

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How this document was developed

An Evusheld Clinical Working Group was convened to develop this document. The Working Group included experts in the areas of infectious diseases, oncology, solid organ transplant, and pediatrics. Working Group members consulted with colleagues in their specialty area for additional input. A draft document was prepared based on the available evidence, drug implementation advice from the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Working Group's clinical expertise. The content of the document was validated by all Working Group members. Working Group members are listed in Appendix A.

Background

Although vaccines protect most people, some immunocompromised populations may have a reduced immune response to COVID-19 vaccination. There is an unmet need for additional protection against COVID-19 infection in patients who are immunocompromised and may have an inadequate response to vaccinations and in patients who have a contraindication to vaccination. Pre-exposure COVID-19 prophylaxis (prevention) may provide some protection for these patient populations.[1,2,3]

What is Evusheld

Evusheld is a combination of two long-acting antibodies (tixagevimab and cilgavimab) that bind to distinct, non-overlapping epitopes of the SARS-CoV-2 spike-protein receptor-binding domain. This potentially blocks interaction with the host cellular receptor, inhibits entry, and neutralizes the virus.[1,2]

Evusheld is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents (≥ 12 years of age weighing at least 40 kg), who have NOT had a known recent exposure to an individual infected with COVID-19 and:

- Who are immunocompromised and are unlikely to mount an adequate immune response to vaccination, **or**
- For whom COVID-19 vaccination is not recommended.[1]

Recent exposure means that the patient has had contact with a confirmed case and is still within the timeframe to develop COVID-19 from that exposure (e.g., 8 days).[4]

Evusheld is administered via two separate intramuscular injections concurrently and is expected to offer protection against symptomatic COVID-19 infection for 6 months or more.[2]

Place in Therapy:

The goal of Evusheld treatment is to reduce symptomatic illness for individuals who are at a high risk of COVID-19 infection.

The primary strategy to protect against severe outcomes from COVID-19 is vaccination. Patients should receive all doses of a COVID-19 vaccine they are eligible for before Evusheld is considered. Evusheld is NOT

a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. At this time, Evusheld is NOT indicated for the treatment of COVID-19, or for the prevention of disease after recent exposure to COVID-19.

Evusheld may provide an additional layer of protection for certain patients. It is strongly recommended that patients continue to limit potential exposure to SARS-CoV-2 through public health measures such as masking and limiting contacts.

Who is eligible for Evusheld in Ontario

Evusheld is currently available in Ontario only to select immunocompromised patients,[5] including:

- Solid organ transplant recipients
- Stem cell transplant recipients
- CAR-T cell therapy recipients, and
- Other hematologic cancer patients undergoing treatment

To be eligible for treatment, patients must:

- Be at least 12 years old
- Weigh at least 40 kg
- Not have a current COVID-19 infection
- Not have a recent COVID-19 exposure

Before receiving Evusheld, eligible individuals should be screened to ensure they are not currently symptomatic or known to be infected with COVID-19. Individuals should also be screened to ensure they have no recent high-risk exposure to a confirmed or probable case of COVID-19 during the close contact's period of communicability. PCR, rapid antigen, and antibody testing are not required prior to receiving Evusheld.[3]

Who may benefit the most from Evusheld

Patient populations that should be prioritized for Evusheld are those who are least likely to mount an adequate immune response to COVID-19 vaccination.[1,2,3] Sub-sets of eligible patients who should be given highest priority for COVID-19 prophylaxis treatment are outlined in Tables 1 and 2. A patient-centred discussion to clarify risks and benefits should be held prior to prescribing Evusheld.[3]

Institutions should put in place the logistics to support and facilitate access to Evusheld, where needed. Within eligible patient categories, clinicians will identify the highest-risk patients for pre-exposure administration of Evusheld. Clinicians will use their discretion regarding which of these patients should receive Evusheld, recognizing that additional risk factors for severe COVID-19 (such as age, comorbidities, and health equity considerations) might influence decision-making.

Pediatric considerations

- **Malignant hematology:** The eligible patient populations are generally like those of adult patients, except for those conditions that do not typically occur among children (e.g., multiple myeloma). For children within these populations, narrower time frames for eligibility are recommended compared to those recommended for adults (Table 1).
- **Solid organ transplant:** Eligibility for pediatric populations aligns with adult populations (Table 2).
- **Equity in access:** In institutions where Evusheld access will be shared among adult and pediatric patients, a process should be in place to ensure equitable access between pediatric and adult patients.

Table 1: Malignant hematology patients to be prioritized for Evusheld[7]

Patient Population	**Recommended Eligibility**	
Tier 1	**Adults**	**Children (≥12 years of age)**
CAR T-cell therapy	• Ideally within 1 year of CAR T-cell therapy • Could be given prior to CAR T-cell therapy	• Within 3-6 months before OR • Within 3-6 months after CAR T-cell therapy
Allogeneic stem cell transplant	• Ideally within 1 year of allogeneic stem cell transplant, or if patient remains on prednisone or other therapy with significant immuno-suppression effects • Could be given prior to allogeneic stem cell transplant conditioning	• Within 3-6 months before OR • Within 3-6 months after transplant
Malignant hematology patients treated with CD-20 inhibitors	• Patients on active treatment, or within 6 months of treatment	• Patients on active treatment, or within 6 months of treatment
Tier 2		
Malignant hematology patients treated with BTK inhibitors or venetoclax	• Patients on active treatment, or within 6 months of treatment	• Patients on active treatment, or within 6 months of treatment
Autologous stem cell transplant	• Ideally within 6 months of autologous stem cell transplant • Could be given prior to autologous stem cell transplant	• Not routinely recommended
Tier 3		
Other malignant hematology patients	• On active treatment, or within 3 months of active therapy	• Based on discretion of subspecialist and within 3 months if considered

Table 2: Solid organ transplant patients to be prioritized for Evusheld[8]

Patient Population	Recommended Eligibility (all patients ≥12 years of age)
Tier 1	
Lung transplant	• All
Recent transplant	• < 6 months
B-cell depletion (Rituximab)	• Within the last 6 months
Plasmapheresis/ATG for rejection (excluding patients with ongoing plasmapheresis)	• Within the last 3 months
Tier 2	
All organs	• Age ≥ 60 years
Tier 3	
All organs	• Age < 60 years

Patients who are immune competent with passive and/or active immunization are least likely to benefit from Evusheld.[3]

Evusheld dosage and administration

Recommended dose and administration:

- 300 mg of Evusheld, administered as two separate sequential intramuscular (IM) injections (150 mg tixagevimab and 150 mg cilgavimab) at different injection sites, preferably one in each of the gluteal muscles.[1]
    - No information is available for administration at other injection sites .[1,6] Evusheld has only been studied as a single dose. There are no data available on repeat dosing.[1]
    - The Health Canada monograph recommends consideration of increasing the dose to 600 mg in regions where the variants BA.1 and BA.1.1 are circulating. In Ontario, these are not the prevalent variants, and the 600 mg dose is not recommended.

Timing of administration:

- There are currently no data on concomitant administration of other treatments, such as chemotherapy. Based on drug interaction information and Evusheld's mechanism of action, it is likely safe to give concomitantly with other treatments; however, due to the lack of data, timing of Evusheld in relation to administration with other treatments will have to be based on clinical judgement.[6]

- In individuals who have received a COVID-19 vaccine, Evusheld should be administered at least 2 weeks after vaccination.[1]
- If a patient is currently eligible for a COVID-19 vaccine dose, they should receive the vaccine before receiving Evusheld. There are no data available regarding COVID-19 vaccination after Evusheld administration.
- Post-COVID-19 infection, the patient should be recovered before Evusheld is administered. Consider waiting for two to three months before administering Evusheld.

Observation period:

- Clinically monitor individuals after injection based on standard protocols for IM injections (e.g., 15 minutes).

Storage and preparation:

- Evusheld is supplied as single-use vials that are stored in the refrigerator. No reconstitution is required. There is 4-hour stability at room temperature.[1]
- Refer to the Evusheld product monograph for further information on storage, dosing, and administration.[1]
- Each antibody requires a single injection in a separate syringe. Care should be taken to ensure that antibodies are not mixed and that the same antibody is not given twice.

Clinical evidence: PROVENT trial

- PROVENT is an ongoing Phase III, randomised, double-blind, placebo-controlled, multi-centre trial assessing the efficacy and safety of an IM 300 mg dose (150 mg tixagevimab and 150 mg cilgavimab) of Evusheld compared to placebo for the prevention of symptomatic COVID-19 in patients who did not have a COVID-19 infection at baseline. The trial was conducted at 87 sites in the US, UK, Spain, France and Belgium.[2]
- 5197 patients were randomised in a 2:1 ratio to receive a single IM dose of either 300 mg of Evusheld (n = 3460) or saline placebo (n = 1737).[1-3]
- The patient population consisted of unvaccinated people 18 years or older who have not had a previous COVID-19 infection. Patients were considered to be at an increased risk of inadequate response to active immunization or increased risk of infection due to location or circumstances, or both. There was a small subgroup of immunocompromised individuals (3.8% of the total study population).[2]
- Patients were excluded if they had a history of COVID-19 infection, a positive COVID-19 test at time of enrollment, or previous receipt of a vaccine or biological agent indicated for the prevention of COVID- 19.[2,3]
- Primary endpoint of symptomatic COVID-19, defined as at least one of the following:
    - No minimum duration: fever, shortness of breath, difficulty breathing; or
    - Present for two or more days: chills, cough, fatigue, muscle aches, body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, diarrhea.[3]

Efficacy

- Compared to placebo, Evusheld reduced the risk of developing symptomatic COVID-19 by 77% (95% confidence interval [CI] 46, 90; p<0.001) at the 3-month analysis. Symptomatic COVID-19 occurred in 8/3441 (0.2%) and 17/1731 (1.0%) patients in the Evusheld and placebo groups, respectively.
- At the 6-month extended analysis, there was an 83% relative risk reduction (95% CI 66, 91; no P-value calculated) with Evusheld. Symptomatic COVID-19 occurred in 11/3441 (0.3%) and 31/1731 (1.8%) patients in the Evusheld and placebo groups, respectively.[2]
- Number needed to treat: 68 patients need to be treated with Evusheld to prevent one case of symptomatic COVID-19 infection over 6 months.[2]
- There were no cases of severe/critical COVID-19, COVID-19-related deaths or hospitalizations in the Evusheld group by the six-month follow-up analysis; there were five cases of severe/critical disease, seven hospitalizations and two COVID-19-related deaths in the placebo group.
- No cases of COVID-19-related deaths were reported with Evusheld.[2]
- Protection against the virus lasted at least 6 months.[2]
- In laboratory testing, Evusheld has been shown to be effective against previously dominant variants of COVID-19. There appears to be some protection against the Omicron variant sublineage BA.2.[1] The effectiveness against future variants of COVID-19 is unknown.

Limitations to the available evidence

- Evusheld prophylaxis has not been studied in patients who have received any doses of a COVID-19 vaccine or in patients with previous history of COVID-19 infection.
- The PROVENT study did not provide efficacy information for the newest variants of concern that are prevalent in Ontario.
- The PROVENT study population did not include patients who are younger than 18 years old.
- The PROVENT study population did not include patients who are pregnant.
- Only a small percentage of the study population were immunocompromised.
- There were a low number of events overall, especially in clinical subgroups.
- Study participants eventually became aware of their randomised assignment in order to consider COVID-19 vaccination. These patients were not included in the longer-term, double-blinded follow-up.
- The role and potential impact of COVID-19 treatments (such as Paxlovid) is unclear.
- The exact duration of response is unknown (at least 6 months). It is unknown whether repeated dosing will be needed, and if the safety profile would remain the same upon repeat dosing.

Side effects/safety

- Evusheld is generally well tolerated. The most common side effects are:
    - Injection site reactions (pain, redness, itching and swelling at site of injection; 1.3%), and
    - Hypersensitivity reaction (rash or hives; 1%).

- Injection-related reactions (includes headache, chills and redness, discomfort or soreness near where the injection was given) were reported in less than 1% of patients.[1]
- No anaphylaxis or serious hypersensitivity reactions have been reported with Evusheld. Serious hypersensitivity reactions, including anaphylaxis, have been observed rarely with other IgG1 monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate treatment.[1]
- In PROVENT, there were more cardiovascular events in the Evusheld arm versus placebo (0.7% versus 0.3%) notably myocardial infarction and cardiac failure.[1-3] Serious thromboembolic events were slightly higher in the Evusheld arm (0.5% versus 0.2%).[1-3] Most patients had cardiac risk factors and/or a prior history of cardiovascular disease. A causal relationship has not been established.[1,2]
- There were no deaths in either arm of PROVENT assessed as being related to the study drug or placebo.[2]

Drug interactions

- No interaction studies have been conducted.[1] Based on mechanism of action and metabolism, it is unlikely that there are clinically significant drug-drug interactions.
- Evusheld is not renally excreted or metabolised by cytochrome P450 enzymes.[1]
- Based on PK modelling, COVID-19 vaccination following Evusheld administration had no clinically relevant impact on the clearance of Evusheld.[1]

Contraindications and precautions

- Evusheld is contraindicated in individuals who have had a severe allergic reaction to Evusheld or any ingredient in Evusheld, including tixagevimab, cilgavimab, L-histidine, L-histidine hydrochloride, or polysorbate 80.[1]
- Due to the increased incidence of cardiovascular and thromboembolic events in patients treated with Evusheld, caution should be used and a discussion of risks and benefits should be held with patients at high risk for cardiovascular or thromboembolic events.
    - Health Canada recommends prescribers consider the risks and benefits before initiating Evusheld in individuals at high risk for cardiovascular or thromboembolic events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular or thromboembolic event. [1]
    - CADTH has advised that Evusheld not be used in patients with a previous history of unstable cardiac conditions (e.g., myocardial infarction, unstable coronary artery disease).[3]
- As with any other intramuscular injection, Evusheld should be used with caution in individuals who have thrombocytopenia or bleeding disorders, or in those who are taking an anticoagulant.[1]
- No information is available for use of Evusheld in pregnancy and breastfeeding. The potential benefits need to be weighed against the potential risks for the pregnant person, fetus, and breastfed child.[1]

How to access Evusheld

Access to Evusheld will be provided to eligible patient populations through select clinics, including cancer centres and transplant sites. Evusheld supply will be received and managed by the hospitals where these clinics are located, and planning for distribution will occur locally. Clinics may work with partners, including primary care providers or community infusion/nursing care clinics, to support care delivery close to home. This network is expected to develop over time to help facilitate additional eligible populations that may be included at a future date.

Questions about access to Evusheld may be directed to the Ontario Health regional contacts listed in Appendix B.

Communication with eligible patients

Proactive communication with priority patients about Evusheld can help to ensure that they receive this preventive antibody therapy before they get sick. This communication can also be an opportunity to recommend COVID-19 vaccine doses that patients may be eligible for. Clinics are strongly encouraged to engage in the following ways with those who may be eligible:

- During appointments
- Via email or telephone
- By updating the clinic's website or online booking portal
- By working with community ambassadors and other partners to support outreach to equity-deserving populations
- By sharing relevant patient medication information

Equity considerations: Certain groups (particularly Indigenous people, Black people, and members of other equity-deserving communities) may be at increased risk of disease progression because of disparate rates of comorbidity, increased barriers to vaccination, and social determinants of health. Sites coordinating access to Evusheld should proactively reach out to groups representing or supporting these populations in order to enhance awareness and facilitate access.

Key resources for health care providers, patients, and caregivers

- Evusheld product description (Health Canada): includes links to resources to obtain more information
- Evusheld consumer information (Health Canada): includes relevant questions and answers for patients and caregivers
- Evusheld patient handout: information about the safe and effective use of Evusheld for patients and caregivers

Appendix A. Evusheld Clinical Working Group members

Name	Title
Christopher Simpson (co-Chair)	Executive Vice President, Medical, Ontario Health; Professor, Department of Medicine, Queen's University; Cardiologist, Kingston Health Sciences Centre
Daniel Warshafsky (co-Chair)	Associate Chief Medical Officer of Health
Upton Allen	Professor, Department of Paediatrics, University of Toronto; Head, Division of Infectious Diseases, SickKids
Vanessa Allen	Medical Director, Provincial COVID-19 Diagnostic Network, Ontario Health; Microbiologist and Infectious Diseases Specialist, Sinai Health / University Health Network Department of Microbiology & Division of Infectious Diseases
Mira Backo-Shannon	Vice President, Clinical Programs, Ontario Health Central
Andrea Crespo	Senior Pharmacist, Systemic Treatment, Cancer Programs, Ontario Health
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Tom Kouroukis	Provincial Head, Complex Malignant Hematology, Ontario Health; Associate Professor, Department of Oncology, McMaster University; Hematologist/Oncologist, Juravinski Cancer Centre
Deepali Kumar	Professor of Medicine, University of Toronto; Director, Transplant Infectious Diseases, University Health Network
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Note: Each member of the Working Group was asked to declare any actual, potential, or perceived conflicts of interest. A summary of disclosures is available here.

Appendix B. Ontario Health regional contacts

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