BC COVID THERAPEUTICS COMMITTEE (CTC)

Clinical Practice Guide for the Use of Tixagevimab/Cilgavimab (Evusheld™)

RECOMMENDATION SUMMARY

Currently, there is a lack of evidence demonstrating a benefit of tixagevimab/ cilgavimab (EVUSHELD™) in preventing hospitalization from COVID-19 particularly in patients infected with variants of concern (e.g., Omicron). Tixagevimab/cilgavimab was evaluated in unvaccinated non-immunocompromised individuals to prevent symptomatic infection with wild-type, Alpha and Delta virus; its role within the present vaccine and therapeutic landscape, especially in immunocompromised individuals who lacked adequate representation in the trial, is unknown (See: Evidence Summary). The theoretical benefit may not be adequately outweighed by the risk of cardiac serious adverse events (SAEs), (See: Cardiovascular SAEs). Further research and real-world evaluation are urgently required. If tixagevimab/cilgavimab is consider for use, it should be on a case-by-case basis where the potential benefit is expected to outweigh any potential risk, the patient needs to be informed about the limitations of the drug, and their values and preferences considered.

The ***case-by-case*** use of tixagevimab/cilgavimab (currently recommended dose of 300mg IM every 6 months; See: Dosing) should be limited to patients who are:

- severely immunocompromised (categorized as Clinically Extremely Vulnerable Group 1) **AND**
- who have no known cardiovascular disease **AND**
- who have additional risk factors or exceptional circumstances that correlate with an extremely high risk of poor outcomes from COVID-19 (See: Who is eligible to receive tixagevimab/cilgavimab?)

Tixagevimab/cilgavimab is not a replacement for vaccination or proven therapies for treatment of COVID-19. Patients should be encouraged to receive scheduled booster doses and be offered therapy if they have symptomatic COVID-19.

What is tixagevimab/cilgavimab (Evusheld™)?

Tixagevimab/cilgavimab is a long-acting monoclonal antibody cocktail initially developed in 2020 that was directed at the spike protein of the wild-type SARS-CoV-2 virus. The intended use was to provide passive humoral immunity prior to the development of COVID-19 vaccinations; however, due to wide-spread vaccination, its role in the current therapeutic landscape has changed and remains uncertain. On April 13, 2022, Health Canada approved tixagevimab/cilgavimab for prevention of COVID-19 in individuals who are immunocompromised and expected to have a reduced response to vaccination or who cannot receive a COVID-19 vaccine.

OPERATIONAL CONSIDERATIONS

Who is eligible to receive tixagevimab/cilgavimab?

The case-by-case use of tixagevimab/cilgavimab should be limited to patients who:

i. Are ***severely immunocompromised*** (categorized as Clinically Extremely Vulnerable Group 1); i.e.:

- are solid organ transplant recipients
- in the past year have received active treatment (chemotherapy, targeted therapies including CAR-T, immunotherapy) for malignant hematologic conditions (e.g., leukemia, lymphoma, or myeloma)
- have received a bone marrow transplant or stem cell transplant in the past 2 years
- are taking immunosuppressants for graft vs. host disease (GVHD), those who have taken anti-CD20 agents or B-cell depleting agents
- those with significant primary immunodeficiency affecting T-cells, immune dysregulation or type 1 interferon defects

AND

ii. Who have ***no known cardiovascular disease*** (i.e., known coronary artery disease, history of myocardial infarction, unstable angina, heart failure, arrhythmia)

AND

iii. Who have ***additional risk factors*** or exceptional circumstances that correlate with an extremely high risk of poor outcomes from COVID-19 (e.g., unable to receive COVID-19 vaccination treatment of COVID-19 is contraindicated, transplant with poor lung graft function, severe GVHD)

Other risk factors may exist and should be determined on a case-by-case basis as per the clinician's discretion. The CTC does not recommend routinely offering tixagevimab/cilgavimab to patients in the CEV 1 category without additional risk factors for hospitalization from Omicron.

Who can prescribe tixagevimab/cilgavimab?

Tixagevimab/cilgavimab is licensed under the Health Canada Food and Drug Regulations. Any health provider with a license to prescribe prescription medications in British Columbia can prescribe tixagevimab/cilgavimab.

Dosing and administration

Recommended dosing: The Canadian monograph recommends standard tixagevimab/cilgavimab dosing of 300mg (150mg each tixagevimab and cilgavimab) IM administered every 6 months. Tixagevimab and cilgavimab are supplied separately and are fully reconstituted; 1.5mL of each component is administered into opposing gluteal muscles. This dose was studied in the PROVENT trial against wild-type, Alpha and Delta virus, and the dose and dosing interval for the BA.2 variant of Omicron were determined through pharmacokinetic studies.

Double dose: In other jurisdictions (e.g., the United States) a 600mg dose has been approved and recommended against Omicron, especially BA. 1 and BA.1.1. However, the manufacturer as stated that the 300mg dose is sufficient to neutralize the BA.2 variant, which is the predominant variant in BC at this time.

Different doses and intervals of administration are currently under evaluation and the dose and/or interval may change. This includes 600mg IM every 6 months, 300mg IM every 3 months and 1200mg IV. CTC and CTRAWG do not recommend doses other than 300mg IM every 6 months at this time.

BA. 4 and BA. 5 variants of concern: Tixagevimab/cilgavimab have also demonstrated reduced binding and neutralization against the BA.4 and BA.5 variants, which are currently circulating in low levels in BC, and may be the next predominant variants in the future. The CTC and CTRAWG are actively monitoring the epidemiology of these variants, as well as any literature that would substantiate a change in dose or doing interval. Guidance will be issued accordingly.

Location: Tixagevimab/cilgavimab can be administered at a physician's office or hospital clinic equipped to give gluteal intramuscular injections. Currently, tixagevimab/cilgavimab cannot be administered in community pharmacies or COVID-19 vaccine clinics. Patients who are hospitalized for non-COVID related reasons may be candidates for tixagevimab/cilgavimab. In such cases, if eligibility criteria have been confirmed, the health authority inpatient pharmacy will dispense tixagevimab/cilgavimab if the order is written. Procedures for this process are currently being drafted; please check with your pharmacy department leadership before prescribing tixagevimab/cilgavimab to inpatients.

Timing

Tixagevimab/cilgavimab is a pre-exposure prophylactic agent and can be administered at a pre-arranged time that is convenient to the patient and provider. It takes approximately 29 days to reach the maximum serum concentration of antibodies after a dose tixagevimab/cilgavimab.

Tixagevimab/cilgavimab should not be used for post-exposure prophylaxis or treatment of mild-moderate COVID as studies for this indication have been negative. It is unknown if tixagevimab/cilgavimab benefits patients who have had COVID-19, especially if they are also immunized. Patients who have tested positive for COVID-19 should wait until they are recovered before receiving tixagevimab/cilgavimab, as with COVID vaccines.

Patients should wait at least 14 days after receiving their last COVID vaccine dose. All vaccine doses, including any overdue boosters, should be given prior to administering tixagevimab/cilgavimab and not be delayed.

Contraindications, cautions and drug-drug interactions

Age and weight: In Canada, tixagevimab/cilgavimab is licensed for adults and adolescents (≥12 years of age weighing at least 40 kg). Persons under 18 years were not included in the PROVENT trial. This labeling is based on pharmacokinetic studies.

Hypersensitivity: Patients with hypersensitivity to tixagevimab/cilgavimab should not receive the product.

Monoclonal antibodies have been shown to be associated with infusion reactions and hypersensitivity reactions including anaphylaxis at rates similar to COVID-19 vaccines. Patients receiving tixagevimab/cilgavimab should be observed for 15 minutes after their injections.

Cardiovascular Disease: In PROVENT, patients taking tixagevimab/cilgavimab experienced more cardiovascular SAEs than those taking placebo (0.56% vs. 0.3%). All patients who experienced cardiac-related hospitalization or death who received tixagevimab/cilgavimab had cardiovascular risk factors; however not all had known cardiovascular disease. The absolute risk of cardiovascular SAEs is low; however, as the benefit of this drug in preventing hospitalization from COVID-19 is theoretical, the risk of tixagevimab/cilgavimab in those with cardiovascular diseases may not outweighed by this benefit.

All trials of tixagevimab/cilgavimab demonstrated a higher rate of cardiac SAEs, including cardiac death in the tixagevimab/cilagavimab arms (PROVENT, STORM CHASER, TACKLE and ACTIV-3). The CTC has conducted further analysis to examine this relationship and the results and publication is pending.

Side effects: General side effects from tixagevimab/cilgavimab are mild and resolve quickly. As with vaccinations, patients can experience pain at the injection site, headache, malaise, and fatigue.

Renal and liver disease: There are no contraindications, dose adjustments or cautions pertaining to renal or liver disease.

Laboratory considerations: There is no laboratory monitoring or baseline laboratory testing that is required for the receipt of tixagevimab/cilgavimab. Participants in the trial of tixagevimab/cilgavimab were seronegative at baseline for the COVID anti-spike and anti-nucleocapsid antibody, and PCR negative. However, as serostatus or quantitative serology is not a strong predictor of vaccine response in conferring protection from COVID-19 hospitalization, such testing is not routinely recommended for the purposes of receiving tixagevimab/cilgavimab.

Cost and dispensing

Tixagevimab/cilgavimab will be dispensed by the BC Product Distribution Centre (PDC), Ministry of Citizens' Services, for all community patients. It is covered under Pharmacare Plan Z. Currently the drug has been procured by the Public Health Agency of Canada and is free of charge, similar to COVID-19 vaccines and antivirals.

Prescriptions should be faxed to 604-941-0532. The drug will be couriered to the location where it will be administered to the patient, or to the patient's home if that is requested. Should the drug be prescribed for a hospital inpatient or a hospital-based clinic (where the order is processed through the hospital pharmacy), the health authority pharmacy will dispense it.

Storage and cold chain

Tixagevimab/cilgavimab is fully reconstituted and ready for injection. It needs to be refrigerated and stored at temperatures of 2-8 degrees Celsius. Couriered drug needs to maintain the cold chain upon arrival. The monograph does not specify how long unopened vials can be stored at room temperature; however states

that pre-drawn syringes can be stored at up to 25 degrees Celsius for up to 4 hours.

Tixagevimab/cilgavimab should not be frozen or shaken. Vials should be kept in the original carton to protect from light. There will be a small volume of unused product remaining - any unused product or waste material should be disposed of in accordance with local requirements.

ADDITIONAL RESOURCES

Patient information about Evusheld can be found in a handout on the BCCDC website: Patient Information about Evusheld.

A 2-page health care provider summary of this guidance can be found on the BCCDC website: Health Care Provider Summary about Tixagevimab/Cilgavimab (Evusheld).

EVIDENCE SUMMARY

Evidence for Tixagevimab/Cilgavimab

Tixagevimab/cilgavimab is currently being evaluated in an ongoing randomized, double-blind, placebo-controlled trial (PROVENT). From November 21, 2020 to March 22, 2021, 5197 patients were enrolled into the trial. The trial ceased recruitment when 30% of patients became aware of their assignment and were unblinded to receive COVID-19 vaccination, triggering the primary analysis. Follow-up is still being conducted.

- Participants: Unvaccinated adults ≥ 18 years who were at higher risk for unfavorable outcomes due to COVID-19 because of risk factors such as age over 60 years or a co-morbidity (e.g., obesity, heart or smoking), or at increased exposure to COVID-19. There were 3.8% of patients considered immunocompromised of whom 2 had hematological malignancies and 1 was a solid organ transplant recipient. Patients had to be seronegative and PCR negative at baseline.
- Baseline Characteristics: Median age was 53 years; patients were mainly white, and 54% were male. The most common risk factor for severe COVID-19 was obesity (41.7%), followed by hypertension (35.9%) and smoking (21%). Eight percent of patients had known cardiovascular disease at a baseline.
- Intervention: Patients were assigned to receive a one-time dose of tixagevimab/cilgavimab 300mg IM or matching saline placebo in a 2:1 fashion.
- Primary Outcome: Symptomatic, PCR-positive COVID-19 infection at a maximum follow-up period of 183 days (median = 83 days) occurred in 8/3441 treated patients vs. 17/1773 placebo recipients (RRR=76.7%; p<0.001).
- Variant of Concern: Approximately half of the COVID-19 cases were caused by the wild-type native virus; the rest of the cases were mainly Alpha and Delta.
- Secondary Outcome: Hospitalizations due to COVID-19 were infrequent and occurred in 0 patients in the treatment arm and 7 patients in the placebo arm. Conversely, 6 patients in the treatment arm visited the emergency department for symptoms consistent with COVID-19 vs. 0 patients in the placebo arm (NS). All infections occurred before the emergence of the Omicron variant.

- Safety: In the overall safety assessment, ~35% of patients experienced an adverse event, most of which were mild. In the appendix, it was apparent that more patient in the tixagevimab/cilgavimab arm experience serious cardiovascular adverse events such as myocardial infarction, heart failure and arrhythmia (23 vs. 5 patients).
- Study Assessment: In addition to the CTC, various assessment groups such as CADTH and INESSS point out shortcomings of the PROVENT trial. While the drug is positioned to offer prophylaxis to immunocompromised patients, such patients were not represented by the trial's population. The drug had no impact on outcomes of interest, namely hospitalizations from COVID-19; symptomatic infection is of little clinical importance especially in the current Omicron wave of the pandemic. The study is out of context with current standard of care which includes multiple-dose vaccination with boosters, and treatments should patients become ill. Lastly, many patients in the trial eventually chose to become unblinded (42%), most to receive vaccination. The receipt of vaccination was not equal between groups (32% of tixagevimab/cilgavimab recipients vs. 50% in the placebo arm). This led to a median participation in the trial of only 83 days, and the population initially randomized may have looked different at the time of the analysis.
- Activity against Omicron: The clinical activity on tixagevimab/cilgavimab against Omicron, especially the emerging BA.4 and BA.5 variants of concern has not been evaluated. In vitro studies demonstrate that tixagevimab/cilgavimab has a 5.3-fold reduction in binding to the BA.2 variant of concern over wild-type virus, most of the binding affinity driven by the neutralization activity of cilgavimab. As the BA.4 and BA.5. variants have arrived in BC and are currently responsible for waves in South Africa, it's also important to note that there is a further 25-fold decrease in binding against these variants.