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BC COVID THERAPEUTICS COMMITTEE (CTC)

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

August Update: REVISED Guidance regarding the use of tixagevimab/cilgavimab for pre-exposure prophylaxis against COVID-19 considering the predominance of the BA 4/5 Variants of Concern in BC.

June Update: Real-world evidence summary of tixagevimab/cilgavimab and update information regarding the use in patients allergic to mRNA vaccines.

RECOMMENDATION SUMMARY

Tixagevimab/cilgavimab is **NOT RECOMMENDED** for pre-exposure prophylaxis, including in severely immunocompromised patients (CEV1).

Currently, there is a lack of high-quality 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 randomized clinical trial, is unclear. Retrospective observational studies show it to be of minimal additive value. (See: Evidence Summary). Tixagevimab is inactive against the currently predominating BA 4/5 variants of concern and cilgavimab has reduced neutralization activity against these variants (See: VoCs); according to real world data, this likely leads to lower serological and clinical activity that cannot be fully overcome by a dose increase (See: Dosing). Further, any theoretical benefit may not outweigh by the potential risk of cardiac serious adverse events (SAEs), (See: Cardiovascular SAEs). Further research and real-world evaluation are urgently needed.

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.

EVIDENCE SUMMARY

Randomized-Control Trial 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.

In-Vitro Studies of Tixagevimab/Cilgavimab against the BA 4/5 Variants of Concern

The clinical activity on tixagevimab/cilgavimab against Omicron, especially the emerging BA.4 and BA.5 variants of concern has not been evaluated. When approving Evusheld, Health Canada deemed the 300mg dose to adequately neutralize BA 2, which was the predominating VoC at the time of the approval.

As of July 2022, the BA.4 and BA.5. variants have arrived in BC and are currently responsible for the current wave of infections with COVID-19 as the predominant variants. Various studies show that there is a significant reduction in binding and a subsequent increase in the inhibitory concentration required to neutralize BA 4/5 which is unlikely to be met using the currently on-label dose. Furthermore, there is a lack of convincing, high-quality data that would support off-label dose increases.

Tixagevimab is inactive against the BA 4/5 variant of concern, and cilgavimab has a substantially decreased affinity towards these two VoCs. Compared to wild-type SARS-COV-2 virus or the Delta Variant of Concern, tixagevimab/cilgavimab has a 95-fold decrease in binding to BA 4/5, which is 10 times lower than against BA 2 and more closely resembles the pharmacodynamics against BA 1, which itself has a 78-fold reduction in binding compared to wild-type virus.

The neutralizing activity has been described in several independent in-vitro studies against viral-like particles (VLPs). A recent study in the NEJM demonstrated the neutralizing concentration of tixagevimab/cilgavimab to be 193 ng/ml, which was 5.6-fold higher than the 34.6 ng/ml than against BA 2. Another in-vivo study quantified the tixagevimab/cilgavimab IC50 as 224 ng/ml, whereas a Japanese study using similar methods assigned the combination product an IC50 of 586 ng/ml, a nearly 124-fold increase over BA 1. Overall, data from independent studies against viral-like particles show heterogeneous and non-reassuring increases in IC50s that vary from one study to the next by as much as 15-fold. In their submission to the FDA which informed the updated provider sheet, the manufacturer argued that the two studies which showed the largest increases in IC50 should not be included in the analysis due to methodological differences (pg. 4), and lower IC50s should be regarded as valid.

Data from the manufacturer cited in the US monograph that references the drugs' activity against BA 4/5 cites that no studies have been conducted to test the activity of the drug against authentic BA 4/5; studies against viral-like-particles (VLPs) show a 65-fold reduction in binding against BA 4/5, a further 13-fold reduction in binding compared to BA 2. In a subsequent FDA assessment, these data also state that assuming physiologically determined penetration of the antibodies into the nasal mucosa, the probability of target

attainment of the 300mg dose of tixagevimab/cilgavimab is 50% at 3 months and <1% at 6 months, and of the 600mg dose is 97% at 3 months and 61% at 6 months. The monograph also reminds that it is not known how pseudotyped VLPs or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome. There are no in-vivo or clinical studies that characterize the activity of tixagevimab/cilgavimab; however, studies of other monoclonal antibodies such as sotrovimab against VLPs vs. authentic virus in vivo show that the latter produces less favorable results.

The Canadian product monograph does not mention the BA 4/5 VoCs nor recommends specific doses or intervals to be used. The monograph states that the 300mg dose may not be sufficiently active against BA 1 but does not mention the activity or dosing against the BA 4/5 VoCs. The FDA has issued a statement that the 300mg dose is inadequate in neutralizing the BA 4/5 VoCs and recommends that the 600mg dose be used. Health Canada has not provided any advice or amended the Drug Product Monograph in lieu of the new VoC; however, the manufacturer rationalizes that clinicians should be able to modify the dose at their discretion based on the predominant VoCs.

Real-World Observational Studies of Tixagevimab/Cilgavimab

There are various retrospective studies of tixagevimab/cilgavimab use in real-world settings. These data add very little to how the drug performs in the target population under current circumstances.

A retrospective matched-control Veterans Affairs study from the US evaluated 1733 Evusheld recipients and 6354 matched controls to determine the association of Evusheld receipt with a composite endpoint of COVID-19 infection, COVID-19 hospitalization, and all-cause mortality. The study has not been critically appraised or published but is available on a pre-print server.

- Participants: Patients receiving Evusheld between January 1, 2022 and April 30, 2022 through the Veterans Affairs clinics, compared to 1:4 propensity-matched controls. Matching was done on the basis of age, sex, vaccination status, chronic conditions, BMI, care assessment needs scores and health care utilization.
- Baseline Characteristics: 91% of patients were male; 77% were White and the median age was 68 years. 74% of patients received 3 doses of an mRNA vaccine; only 5% did not have a record of a COVID immunization. 92% of patients were considered immunocompromised on the basis of a diagnosis or a receipt of immunosuppressants. Mild-severe immunocompromise was included in that definition. ~30% of patients had cancer, ~20% had chronic kidney disease, 18% had COPD and 58% had hypertension. Some imbalances in the baseline characteristics are apparent.
- Comparisons: Patients who received tixagevimab/cilgavimab were compared to those who did not receive the drug. Patients received 300mg until Feb 24th, and 600mg thereafter. Those given 300mg were offered a top-up. Patients were included in the analysis if they received at least one dose of the drug.

- Baseline prevalence of the composite outcome: Patients included in the analysis were first compared in the 4-month period before January 1st before Evusheld was available. Patients eventually treated with Evusheld had a 25% lower baseline prevalence of the primary endpoint vs. controls (0.6% vs. 0.8% per month). This difference widened to 35% in the period after Evusheld was made available (0.9% vs. 1.4%); however, despite matching, patients who were treated with Evusheld were lower risk patients despite propensity score matching.
- Primary Outcome: After Evusheld was made available, patients who received Evusheld had a lower rate of the primary endpoint (1% vs. 3.2%, HR 0.31, CI 0.18-0.53).
    - The primary endpoint was largely driven by all-cause mortality (<0.5%* vs. 2%). Even if all severe COVID-19 cases requiring hospitalization led to death in the patients in the study, all-cause mortality not explained by COVID or mitigated by Evusheld was still. <0.5%* (*actual rate not calculated due to small numbers) vs. 1.5%. This highlights the imbalance of risk of the compared patient populations that is not related to COVID-19 or Evusheld
    - The study reported that COVID-19 infection (confirmed by PCR or RAT) was lower in the Evusheld arm (<0.5% vs. 1%); however, COVID-19 infection in the Omicron wave globally, including in BC, was thought to occur in over 50% of the population. As such, the contribution of COVID-19 infection to the primary endpoint is not valid. Furthermore, there are many biases that influence access to PCR testing and reporting of the test results.
    - COVID-19 related hospitalization was reported to occur in <0.5% of Evusheld recipients vs. 0.5% of those who did not receive Evushled (HR 0.13, CI 0.02-0.99). This hospitalization rate is lower than the average hospitalization rate of all BC patients, and about 10-fold lower than what is seen in immunocompromised patients in BC. This low hospitalization rate is likely drive by access to and receipt of treatment for COVID-19. Unfortunately, the proportion of patients in each arm that received treatment was not reported and not accounted for in the matching or analysis. Access to Evusheld is likely a predictor of access to therapy in general; hence, the difference in hospitalization may have been driven by the imbalance of access and receipt of treatments like Paxlovid or sotrovimab, which are all considered standard of care in the US in these populations.
    - The study also showed that those who were vaccinated with three doses experienced these endpoints less frequently (2.8% vs. 3.7%). The COVID-19 hospitalization rate difference would not be statistically significant, with the confidence interval crossing 1.0, if only fully vaccinated individuals were analyzed.
- Overall, the CTC concluded that based on this study, Evusheld's ability to lower COVID-19 hospitalization was not convincing despite a large sample, and an absolute risk difference of < 0.5% seen in the context of therapeutics has little clinical significance in this population.

Various smaller studies have evaluated the impact of Evusheld in special populations, including those with hematological malignancies.

- A small observational study of 52 patients (half were HSCT recipients) who received Evusheld 300mg (150mg each component) and 600mg (N=22) who were either topped-up or given 600mg directly. The 300mg dose did not produce titers that were high enough to neutralize Omicron in 30/47 patients. Of the 10 patients given 600mg, 9 had significantly higher antibody titers; however, the study reported that "they remained heterogeneous…[and]…notably did not correlate with neutralizing capacity against Omicron". Two patients developed COVID-19 in the 2-month follow-up period despite receipt of Evusheld (both were treated with sotrovimab and recovered).

Evusheld has also been evaluated in cohorts of kidney transplant recipients, yielding mixed results.

- An observational study of kidney transplant recipients from France evaluated 572 KTRs with low IgG titres post COVID-19 vaccination. 412 patients received Evusheld and 168 did not. Those who received Evushled were found to have lower symptomatic COVID-19 infection rates (5.3% vs. 26.9%) and hospitalization rates (1.5% vs. 9.4%). There were minimal baseline characteristics given and no adjustment for imbalances or confounders was performed.
- Another observational study from France evaluated 63 KTRs who received Evusheld 300mg who have not been previously infected with COVID-19. Those who had anti-nucleocapsid antibodies indicating previous infection served as positive controls, and those who did not receive Evusheld and had no history of infection served as negative controls. At 29 days post injection, 6/63 had antibodies that were able to neutralize Omicron, compared to 10/14 who were previously infected with Omicron. The study reported that antibody titers were low and heterogeneous. 7 patients who received Evusheld developed COVID-19 and 2 were hospitalized.
- Another study by the same authors showed that of 416 KTRs treated with 300mg of Evusheld, 39 developed COVID-19 and 35% of the patients (N=14) required hospitalization. 12/15 patients who were tested for serology had antibody levels insufficient to neutralize Omicron, concluding that the 300mg dose provides insufficient protection against the virus and hospitalization.

PRACTICAL CONSIDERATIONS

Evusheld is a unique prescription drug as it is procured by the Public Health Agency of Canada, distributed centrally and provided free of charge to patients. While tixagevimab/cilgavimab is not recommended by way of this guidance, clinicians retain autonomy in prescribing drugs available in British Columbia and hence have the right to be aware of the practical considerations surrounding its use. ***The operational considerations are provided for transparency and should not be misconstrued as encouragement to prescribe the product.***

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

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 4/5. This dose has been determined by in-vitro evaluation of binding of tixagevimab and cilgavimab to viral-like particles (VLPs). There are no data that evaluate the activity of tixagevimab or cilgavimab against authentic SARS-COV-2 or any clinical data, including in animals, that characterize its activity in vivo. Health Canada has not provided any guidance as to the dosing against BA 4/5 VoCs.

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. As per the US Monograph, the 600mg IM dose achieves a pharmacokinetic target attainment of 98% at 3 months after injection but only 61% at 6 months.

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.

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.

Cross-reactivity with mRNA Vaccines: On May 26th, the FDA issued an update stating that those allergic to mRNA vaccines may also be allergic to Evusheld. Most allergic reactions after the mRNA vaccines are due to polysorbate 80 and polyethylene glycol (PEG). Evusheld contains polysorbate 80, which is also structurally similar to PEG. Patients with hypersensitivity to mRNA vaccines should not be given Evusheld without allergist consultation.

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.

If choosing to prescribe, 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.

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.