Therapeutics Technical Advisory Group | Te Rōpū Haumanu Kowheori-19

Update for health professionals: Use of Evusheld for the Prevention and Treatment of COVID-19

Date: 29 August 2022
Updated: 21 December 2022

The Therapeutics Technical Advisory Group (Therapeutics TAG) was established by the Ministry of Health in August 2021 to provide expert advice on existing and emerging medicines for use in the management of COVID-19.

Update relating to new circulating SARS-CoV-2 variants:

- Evusheld™ (tixagevimab/cilgavimab) is currently predicted to have neutralising activity against fewer than 50% of currently circulating SARS-CoV-2 variants. Therefore, most eligible people are not anticipated to benefit from treatment, unless there is evidence their infection is caused by a variant predictably neutralised by Evusheld.
- The Therapeutic TAG advises, if possible, to let patients who have had Evusheld™ know that the benefit has diminished, they are less protected than before and if they develop symptoms, to test and seek treatment.
- Pharmac has approved funding for administration of Evusheld™ as treatment. This would typically be under the oversight of an Infectious Diseases or other specialist familiar with Evusheld™, for a suspected or confirmed susceptible SARS-CoV2 variant.
- Therapeutic TAG advises that Paxlovid™ (or remdesivir) are preferable treatments to Evusheld.
- There is no evidence to suggest a benefit from prescribing both an antiviral and antibody treatment routinely.

The Ministry of Health, Pharmac, Medsafe, the Therapeutics TAG and others are working collaboratively to ensure ongoing support of medicines for the prevention and treatment of COVID-19.

Although COVID-19 vaccines provide enhanced protection to most people, some severely immunocompromised people remain vulnerable to COVID-19 despite vaccination. These people may benefit from Pre-Exposure Prophylaxis (PrEP) with Evusheld: a long-acting combination of anti-SARS-CoV-2 monoclonal antibodies (MAb). [1] MAbs may have a role in prevention and treatment of COVID-19 infection in those lacking their own humoral immune response. A number of MAbs have been produced and made available for clinical use, targeted against the SARS-CoV-2 spike protein, although their neutralising activity varies for different variants of concern.

New Zealand has an initial supply of Evusheld that is currently available for use.

This document aims to provide a reference to support clinicians prescribing and administering Evusheld. It covers the current recommendations for use in a New Zealand context, information relating to contraindications, existing evidence from clinical trials, effectiveness against new variants, and references to frequently asked questions.

Table of Contents

Background 2
Current recommendations in New Zealand 3
Eligible population 3
Recommended Dose 5
Administration of Evusheld 5
Adverse effects 5
Prioritisation within eligible populations 6
Contraindications and precautions 6
Evusheld timing in relation to COVID-19 vaccination and infections 8
Summary of evidence 8
PROVENT Trial 8
STORM CHASER trial 9
TACKLE trial 9
ACTIV-3 trial 10
Effectiveness against Omicron subvariants 10
Frequently asked questions 11
Abbreviations 11
References 12

Background

AstraZeneca's Evusheld (otherwise known as AZD7442) is a combination of two long-acting antibodies: tixagevimab and cilgavimab. [2] These have been derived from donated B-cells of patients who have recovered from SARS-CoV-2 infection. [3] Both tixagevimab and cilgavimab are recombinant human IgG1κ monoclonal antibodies that have been engineered with amino acid substitutions in the Fc region to significantly extend their half-lives: estimated to be 90 days. [3, 4] Tixagevimab and cilgavimab each target distinct and non-overlapping epitopes of the SARS-CoV-2 spike protein located in the receptor binding domain. The antibodies neutralise SAR-CoV-2 infections by binding to the spike protein and blocking interactions between the virus and the host's cellular receptors.[3]

Evusheld is mainly intended for people who are immunocompromised where it is considered they would not (or have not) develop(ed) a meaningful antibody response to vaccination. Even though this group is somewhat different from the registration trial participants (which had small numbers of immunocompromised participants), clinical experience in Aotearoa New Zealand has been that people who are immunocompromised and do not respond to vaccination optimally (e.g., transplant patients) have been some of the most challenging to treat and have had poorer outcomes than immunocompetent age-

matched comparators. Evusheld can provide passive immunity to these patients and may improve COVID-19 outcomes.

For all immunocompromised patients in whom vaccination is recommended, a three-dose primary series should be completed prior to PrEP with Evusheld. For more information on for whom Evusheld is intended, refer to the indications section of this report.

Medsafe are considering approval of Evusheld in two phases:

1. as PrEP for COVID-19
2. for treatment of patients with COVID-19.

The evidence supporting PrEP has already been assessed and provisional approved, while the evidence for use of Evusheld post-exposure to prevent infection or as treatment is still under evaluation. Further guidance will be given on the use of Evusheld post-exposure or as treatment. Except where otherwise stated, this memo discusses the use of Evusheld as a PrEP.

Current recommendations in New Zealand

Eligible population

Evusheld is indicated for use as PrEP against severe COVID-19 in people **≥ 12 years and ≥ 40 kg weight** who meet the following Pharmac access criteria:

All of the following

1. **Patient does not currently have SARS-CoV-2 infection**

   AND

2. Either

   2.1. **Patient is severely immunocompromised** and considered to **be at risk of inadequate immune response to SARS-CoV-2 vaccination or infection** due to any of the following clinical situations:

   2.1.1. heart or lung transplant recipient (any time frame)

   2.1.2. other solid-organ transplant with any of the following:

   2.1.2.1. transplant received within last 12 months

   2.1.2.2. received induction immunosuppressant treatment (any time frame)

   2.1.2.3. received maintenance immunosuppressant treatment that includes mycophenolate mofetil (any time frame)

   2.1.2.4. treated for graft rejection within the past 12 months

   2.1.3. allogenic haematopoietic stem transplant recipient with any of the following:

   2.1.3.1. transplant received within last 12 months

   2.1.3.2. has chronic graft vs host disease

2.1.3.3. requires significant ongoing immunosuppression for another reason

2.1.4. autologous haematopoietic stem cell transplant received in the last 12 months

2.1.5. multiple myeloma on active and/or maintenance treatment

2.1.6. combined primary immunodeficiency syndromes (including Severe Combined Immunodeficiency (SCID))

2.1.7. common variable immunodeficiency (CVID) with additional T-cell defects, past opportunistic infection or requiring immunosuppressive therapy

2.1.8. diagnosed humoral immunodeficiency with baseline IgG<3g/mL

2.1.9. HIV with a CD4 T lymphocyte cell count <200 cells/mm^3

2.1.10. person who is receiving:

2.1.10.1. potent B-cell or T-cell depleting therapy within the previous 12 months or planned to receive within two weeks of tixagevimab and cilgavimab administration*

(*potent B-cell or T-cell depleting therapy such as rituximab, obinutuzumab, ocerelizumab, bendamustine, fludarabine, cladribine, alemtuzumab,anti-thymocyte globulin, CamPath antibody treatment, anti-B-cell bispecific, CAR T-cells or BiTE antibody)

2.1.10.2. a B-cell inhibitor (e.g., venetoclax or Bruton tyrosine kinase inhibitor)

2.1.10.3. ruxolitinib

2.1.10.4. regular 3-4 weekly intravenous or subcutaneous immunoglobulin

2.1.10.5. sphingosine 1 -phosphate receptor modulator therapy (e.g., fingolimod) within previous 12 months

2.1.10.6. high dose cyclophosphamide (.1g/m^2) within previous 6 months

2.1.11. history of previous persistent SARS-CoV-2 infection (defined as a laboratory confirmed diagnosis of persistent SARS-CoV-2 infection persisting 20 days) that has since resolved

OR

2.2. **Person is both**:

2.2.1. not able to be vaccinated against COVID-19 due to medical contraindication (e.g., a history of sever adverse reaction to COVID19 vaccine or its components

AND

2.2.2. is considered at high risk of severe illness from COVID-19 infection.

Recommended Dose

Based on currently available information, **our recommended dose for PrEP is 600mg intramuscularly (300 mg tixagevimab + 300 mg cilgavimab).**

Using data from the PROVENT study, the Food and Drug Administration (FDA) initially authorised an Emergency Use Authorization (EUA)dosage of Evusheld at 300 mg (150 mg of each antibody), however subsequent evidence suggests an increased dose of 600 mg (300 mg per antibody) is more appropriate to provide protection from Omicron subvariants (specifically BA1 and BA1.1). Subsequently, the manufacturer (AstraZeneca) and FDA have amended their recommendation to support a 600mg dose.

Medsafe has already approved the use of the 300 mg (150 mg per antibody), however the 600 mg (300 mg per antibody) dose is not yet approved. An application has been submitted and is under review. The Pharmac Access Criteria has funded a single dose of 600 mg (300 mg per antibody), and can be given with informed consent.

Repeat dosing is not currently funded by Pharmac.

Administration of Evusheld

Evusheld is supplied in a carton which contains two separate single-use vials that do not require reconstitution. These contain one of each of the antibodies (tixagevimab and cilgavimab) and should be administered as separate single injections. These are to be administered sequentially as intramuscular injection into different sites. The preferred injection sites are the gluteal muscles. Care must be taken to ensure the patient receives equal doses of BOTH antibodies.

> ***Note:*** one carton contains one 300 mg dosage (150 mg of each antibody). To administer a 600 mg dose, two cartons (2x 150mg of each antibody) need to be used.

Evusheld requires storage in the refrigerator but is stable for 4 hours at room temperature.

Clinical observation of the patient is recommended for 15 minutes following injection.

Information relating to intravenous administration has been developed the Notes for Injectable Drugs (NOIDs) and can be found here (link).

Adverse effects

Like other monoclonal antibody treatments, Evusheld is generally well tolerated. In registration trials, there was no increase in the proportion of patients treated with Evusheld who reported adverse events compared with placebo. Reported adverse effects include:

- **Injections site reactions** associated with intramuscular administration (1.3% in PROVENT, 2.4% in TACKLE).
- Other commonly reported adverse effects in PROVENT included **headache, fatigue and cough** (>3%).
- **Hypersensitivity and infusion reactions**: As with other monoclonal antibody treatments, hypersensitivity reaction including anaphylaxis have been observed (one patient in the PROVENT

trial, none in TACKLE). Similarly, infusion reactions may occur with intravenous administration of Evusheld, however the rates of infusion reactions reported in ACTIV-3 were no different between patients receiving Evusheld compared with placebo infusions.

- **Cardiovascular and thromboembolic events:** A higher proportion of Evusheld recipients in PROVENT and TACKLE experienced cardiovascular and thromboembolic adverse effects than placebo: predominantly myocardial infarction and heart failure. This difference was not observed in STORMCHASER or ACTIV-3. All events occurred in people with risk factors or pre-existing cardiac disease. Although a causal relationship has not been established, several health authorities have advised against use in patients at very high risk of cardiovascular disease.

More information about adverse events is available on the Medsafe, FDA and UK MRHA datasheets.

Any observed adverse effects of Evusheld should be reported to CARM.

Prioritisation within eligible populations

While all patients eligible for Evusheld are anticipated to benefit from treatment, due to practical restrictions on the number of patients who can be treated at any time within existing healthcare resources, initial doses should be prioritised to patients who are likely to gain the most benefit.

While careful prioritisation for patients with haematologic malignancy and solid organ transplant recipients is required, the following general principles should be considered:

- Duration and depth of immunocompromise. Patients with longer-lasting, deeper immunosuppression are likely to gain more benefit from Evusheld than patients with short-lived or less profound immunosuppression. Examples might include administering Evusheld to patients who have recently received Rituximab or those who are predicted to require ongoing Rituximab, before patients who had a single dose of Rituximab 11 months ago.
- Older age is the strongest risk factor for severe COVID-19 and death. When considering otherwise similar patients, older age should be prioritised.
- Other 'traditional' risk factors for severe COVID-19 should be considered, and priority given to otherwise similar patients with more severe comorbid disease or a higher burden of comorbidities.

Additionally, while we do not advocate for routine SARS-CoV-2 serology testing as part of the administration of Evusheld, we recognise that if a patient's recent SARS-CoV-2 serology results were known, it may be reasonable to prioritise patients who have demonstrated a poor serologic response to a three-dose primary course of vaccination over those with robust serologic response.

Contraindications and precautions

Evusheld is not recommended for use in people that are immune competent and/or considered sufficiently immunised as these patients are less likely to benefit from it. [5]

According to the Medsafe datasheet , Evusheld is contraindicated in individuals with a history of severe hypersensitivity reactions (including anaphylaxis) to the active substances or excipients of Evusheld.

This includes:

- active ingredients tixagevimab and cilgavimab
- L-histidine, L-histidine hydrochloride, or polysorbate 80.

Additionally, special precautions have been listed for use in patients with:

- Clinically significant bleeding disorders
  - As with any other intramuscular injections, Evusheld should be used with caution in patients with thrombocytopenia or coagulation disorder.
  - Intravenous infusion of Evusheld should be offered in preference to intramuscular injection in patients with severe thrombocytopenia or coagulation disorders that cannot be ameliorated to reduce risk of intramuscular haematoma [1]
- High risk of cardiovascular and/or thromboembolic events
  - While a causative relationship between Evusheld and these adverse events has not been confirmed, people with a significant history of, or assessed to be at very high risk of cardiovascular or thromboembolic events should receive Evusheld only after careful consideration. In general, Evusheld should be avoided in such people unless the risk of severe COVID-19 outweighs the potential risk of cardiovascular or thromboembolic events in the following 6 months.

    For those patients with significant thrombocytopenia (i.e., Platelets < 70 x 10^9/L) those with known coagulopathies, and those on long-term anticoagulation**, specialist haematologist advice should be sought** before IM administration of Evusheld. Some patients may require either a platelet transfusion, specific coagulation factor administration or temporary cessation of their anticoagulation prior to receiving Evusheld.
- Pregnancy and lactation
  - There are limited data for the use of tixagevimab and cilgavimab in pregnant people. Non-clinical reproductive toxicity studies have not been performed with tixagevimab and cilgavimab. In a tissue cross-reactivity study with tixagevimab and cilgavimab using human foetal tissues, no binding was detected.
  - Evusheld should only be used during pregnancy if the potential benefit outweighs the uncertain risk for the mother and the foetus.
  - It is not known whether tixagevimab and cilgavimab are excreted in human milk. Exposure to the breast-fed child cannot be excluded. The developmental and health benefits of breast-feeding should be considered along with the parent's clinical need for Evusheld and any potential adverse effects on the breast-fed child from Evusheld.

No Interaction studies have been conducted but Evusheld is not expected to undergo metabolism by hepatic enzymes or renal elimination.

Evusheld timing in relation to COVID-19 vaccination and infections

It is possible that Evusheld might reduce the immune response to vaccination. For the use of Evusheld as PrEP, we agree with advice given by some international advisory bodies (including the FDA and Ontario Health) that:

1. if a patient is eligible for COVID-19 vaccination, completion of a three-dose primary course should generally be prioritised prior to receiving Evusheld
2. patients who have received a COVID-19 vaccine should wait at least 2 weeks before receiving Evusheld

Eligible patients who have recently recovered from COVID-19 are less likely to be re-infected than similar uninfected patients. As such, the additional benefit of Evusheld might be lower in the months after recovery. For this reason, clinicians caring for patients recently recovered from COVID-19 should consider deferring Evusheld for 2-3 months after clinical recovery.

When planning timing of Evusheld in relation to vaccination and recent COVID-19, clinicians should consider an individual's medium-term risk of new or repeat COVID-19 infection, anticipated immunocompromise during this time and likelihood of response to vaccination. In most situations completion of a three-dose primary vaccine series should be the first priority, with subsequent administration of Evusheld. However, in some situations (e.g. immediately after haematopoietic or solid organ transplantation) it may be reasonable to recommend Evusheld immediately and defer completion of primary vaccine series until the period of deepest immunosuppression has passed.

Summary of evidence

PROVENT Trial

PrEP Trial: The PROVENT trial is an ongoing phase 3, double-blind, randomised, 2:1 placebo-controlled trial. [2] This was a multi-centre trial, with 87 international sites in locations including US, UK, Belgium, Spain and France. [6] The purpose of this trial was to evaluate the safety and efficacy of a single dose of tixagevimab plus cilgavimab at preventing symptomatic, PCR-confirmed COVID-19 during a follow up period of 183 days. [2] Participants were adults (18 years and above) who were unvaccinated against COVID-19 and had increased risk of severe disease (e.g., prespecified comorbidities or above 60 years old). The study excluded people with confirmed history of COVID-19 or positive antibody result at screening. Participants who tested negative for SARS-CoV-2 by PCR tests at baseline were either administered a single, 300mg intramuscular (IM) dose of Evusheld (150mg tixagevimab, 150mg cilgavimab; n=3,460) or placebo (n=1,737). [2] Participants could be unblinded and receive a COVID-19 vaccine, resulting in approximately 30% knowing their randomised assignment before primary analysis.

Efficacy: Prior to unblinding, 0.2% of the treatment group reported symptomatic COVID-19 infections compared to 1.0% in the placebo: a relative risk reduction (RRR) of 76.7% for infections in the treatment group. Only primary endpoints that were prior to participants' vaccination were included in the study. This had a median follow up time of 83 days and showed an 82.8% reduction of symptomatic COVID-19 in high-risk people. [2]

Safety: In the treatment group, 35.5% of participants reported at least one adverse effect, compared to 34.2% in the placebo group. Most of these were mild or moderate in severity. During the study, there were

five cases of severe or critical COVID-19 and two COVID-19 associated deaths. These were all in participants within in the placebo cohort. [2]

Over 75% of participants in the PROVENT study were high risk for severe COVID-19 due to co-morbidities, indicating this treatment is appropriate for immunocompromised people. [6]

On 08 December 2021, the FDA authorised the use of Evusheld as an Emergency Use Authorization (EUA) medicine based on primary data from the PROVENT trial. [7]

One important limitation of this study is that this data was collected prior to Omicron. For more details on how this may affect Evusheld see the effectiveness against new variants section. Another limitation of the trial is that it recruited only unvaccinated participants and only 11% of participants were immunocompromised. Therefore, it is hard to extrapolate these findings to estimate real-world effectiveness for vaccinated, immunocompromised people in the era of Omicron subvariant circulation.

STORM CHASER trial

Treatment Trial: The STORM CHASER was a phase 3, randomised double-blind placebo control trial completed across multiple sites. It assessed the efficacy and safety of Evusheld using the 300 mg dose for post-exposure prevention of COVID-19. The trial had 1,121 participants who were all 18 years or older with a confirmed COVID-19 exposure within the previous eight days. The trial found that the treatment group had a reduced risk of symptomatic COVID-19 infection, with an estimated 33% (95% CI: -26% to 65%) compared to placebo, however this was not statistically significant. As a result, the trial did not show efficacy as post-exposure prevention. Nevertheless, patients who did not get infected after exposure to close contacts had lower rates of new infection outside of the exposure incubation period, adding evidence in support of Evusheld role for pre-exposure prophylaxis. [8]

TACKLE trial

Treatment Trial: The TACKLE trial was a randomised double-blind, 1:1 placebo-controlled phase 3 trial. [9] It aimed to evaluate the safety and efficacy of treatment of early COVID-19 with tixagevimab and cilgavimab to prevent progression to severe disease or death. The trial was conducted over 95 sites including in USA, Europe, Latin America and Japan. Participants included non-hospitalised unvaccinated adults (18+ years) who had a confirmed SARS-CoV-2 infection test collected 3 days or less prior to enrolment. The participants were enrolled between January and July 2021, meaning that this study was conducted prior to the emergence of Omicron. Viral sequencing confirmed that Alpha (B.1.17) was the most prevalent variant, accounting for 60% of the study. Other variants included Gamma (20%), Delta (15%), Lambda (5%), Mu (1%) and Beta (<1%). The Evusheld dosage used was 600 mg IM as a single dose.

Efficacy: Severe COVID-19 progression or death was reported in 4% of the treatment cohort (n=407) compared to 9% of the placebo (n=415): a relative risk reduction of 50.5% (95%CI, 14.6% to 71.3%, p=0.0096).

Safety: Adverse events were seen in 29% of the treatment cohort and 36% in the placebo, however almost all of these were either mild or moderate. In the tixagevimab and cilgavimab treated cohort, 3 deaths were reported while 6 were reported in the placebo cohort. [9]

These authors conclude that statistically and clinically significant reduction in death and progression to severeCOVID-19 was provided following a 600mg dose of tixagevimab and cilgavimab.

ACTIV-3 trial

Treatment Trial: ACTIV-3 was a randomised double-blind, 1:1 placebo-controlled phase 3 trial of COVID-19 treatment. It assessed the impact on likelihood of sustained recovery or death of tixagevimab and cilgavimab compared with placebo in adults hospitalised with COVID-19, in addition to standard of care (including remdesivir). [10] The trial was conducted over 81 sites including in USA, Europe, Singapore and Uganda. Participants were hospitalised, symptomatic adults with COVID-19 and up to 12 days of symptoms. Participants received either an intravenous 600mg dose or placebo. Patients were excluded if they had acute organ failure.

Efficacy: The study reported estimated cumulative incidence of sustained recovery for 89% of participants treated with tixagevimab and cilgavimab compared to 86% in the placebo group. Mortality was reduced in cohort treated with tixagevimab and cilgavimab (9%) compared to placebo (12%), with a hazard ratio [HR] of 0.70 (95% CI 0.50-0.97), p=0.032.

Safety: Composite safety was 25% in the treatment group compared to 30% in the placebo group. Both groups reported 5% experiencing SAE.

Participants were recruited from February to September 2021, when Delta was the predominant variant in circulation. Overall, the study concluded that the use of use of tixagevimab and cilgavimab did not improve the time to sustained recovery, however the treatment was safe and reduced mortality by 3%. [10]

Effectiveness against Omicron subvariants

At the time of writing, Omicron subvariant BA.5 is dominant in New Zealand, with ESR reporting that this accounts for over 90% of all community cases of the week ending 25 August 2022. [11] Other Omicron variants including BA.4, BA.2, BA.1.12.1 and BA.2.75 are also currently circulating. [12, 13] For the most recent updates, refer to the latest ESR report.

Reduced effectiveness against new variants is the primary reason for the increased dose of 600 mg Evusheld being licensed for PrEP. Several in-vitro studies suggest that the neutralising activity of Evusheld is likely to be lower for Omicron subvariants than for the Delta variant. This has been reported as decreased by approximately 5-fold against BA.2 and BA.2.12.1, 33-fold for BA.4 and 65-fold against BA.5. [14] Additionally, a study in Nature (March 2022) reported neutralisation against BA.1 and BA.2 was markedly decreased, with neutralising titres decreased by 344-fold and 9-fold respectively compared to in Delta. [15] A preprint in medRxiv has also assessed the neutralisation capacity of Evusheld against BA.2 and BA.5 variants. It found that Evusheld retained activity against BA.2 but a drop in potency was observed for BA.5. This study said this is expected due to the significant mutations against the receptor binding domain in the latter Omicron variants, as this is the target site for Evusheld. Although some retention of neutralising ability of Evusheld is promising, the trend towards lower potency with new variants will need monitoring. [16]

Although neutralising ability against Omicron is significantly decreased, the FDA has used pharmacokinetic modelling, originally against BA.2 but subsequently for BA.5/BA.5 subvariants. this has suggested that PrEP with 600 mg Evusheld still provides sufficient activity against these variants for 6 months following

administration. [14] Continued monitoring of emerging variants and their neutralising activity of Evusheld is required to ensure the appropriate use of Evusheld.

Several retrospective cohort studies have been published supporting retained efficacy of Evusheld in the Omicron era. A group from Boston reported the protection of Evusheld treatment (300mg dose) against breakthrough infection in vaccinated solid organ transplant recipients (SOTRs). The authors reported that the treated SOTR group had 5% occurrence of breakthrough infection compared to 14% in the control cohort, which was statistically significant ($p<0.001$). [17] Another report from a French renal transplant group suggested reduced rates of hospitalisation and death among patients who received Evusheld during the French BA.1 and BA2 surges of 2022. [18]

Frequently asked questions

The FDA and Department of Health, Australia have both produced documents on the FAQ on the EUA of Evusheld for PrEP of COVID-19.

Abbreviations

CADHT: Canadian Agency for Drugs and Technology in Health

EUA: Emergency Use Authorization

FDA: Food and Drug Admission

Fc region: Fragment crystallizable region

IM: Intramuscular

IV: Intravenous

PrEP: Pre-exposure prophylaxis

SAE: severe adverse events

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

References

1. Ontario Health. *Information about Evusheld (Tixagevimab and Cilgavimab) Reference for health care providers who may be prescribing or administering Evusheld*. 2022 09 May 2022]; Available from: https://www.ontariohealth.ca/sites/ontariohealth/files/2022-05/Information%20for%20health%20care%20providers%20-%20Evusheld.pdf.
2. Levin, M.J., et al. *Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19*. New England Journal of Medicine 2022 2022/06/09 [cited 386 23]; 2188-2200]. Available from: https://doi.org/10.1056/NEJMoa2116620.
3. AstraZeneca. *Evusheld™ receives Health Canada approval for pre-exposure prophylaxis (prevention) of COVID-19 in immune-compromised individuals*. 2022 14 April 2022; Available from: https://www.astrazeneca.ca/en/media/press-releases/2022/evusheld--receives-health-canada-approval-for-pre-exposure-proph.html.
4. European Medicines Agency (EMA). *Evusheld (tixagevimab / cilgavimab) Annex 1 Summary of Product Characterisitics* 2022; Available from: https://www.ema.europa.eu/en/documents/product-information/evusheld-epar-product-information_en.pdf.
5. AstraZenica. *CADTH Drug Implementation Advice: Tixagevimab and Cilgavimab (Evusheld) [Internet].* . 2022; Available from: https://www.cadth.ca/sites/default/files/hta-he/HD0008-Evusheld.pdf.
6. AstraZeneca. *Evusheld significantly protected against symptomatic COVID-19 for at least six months in PROVENT Phase III trial in high-risk populations*. 2022 20 April 2022; Available from: https://www.astrazeneca.com/media-centre/press-releases/2022/evusheld-significantly-protected-against-symptomatic-covid-19-for-at-least-six-months-in-provent-phase-iii-trial-in-high-risk-populations1.html.
7. Food and Drug Administration (FDA). *Coronavirus (COVID-19) Update: FDA Authorizes New Long-Acting Monoclonal Antibodies for Pre-exposure Prevention of COVID-19 in Certain Individuals*. 2021 08 December 2021; Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-long-acting-monoclonal-antibodies-pre-exposure.
8. AstraZeneca. *Update on AZD7442 STORM CHASER trial in post-exposure prevention of symptomatic COVID-19*. 2021 15 June 2021; Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html.
9. Montgomery, H., et al. *Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial*. The Lancet. Respiratory medicine 2022; Available from: https://www.unboundmedicine.com/medline/citation/35688164/Efficacy_and_safety_of_intramuscular_administration_of_tixagevimab-cilgavimab_for_early_outpatient_treatment_of_COVID-19_(TACKLE):_a_phase_3,_randomised,_double-blind,_placebo-controlled_trial.
10. ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. *Tixagevimab–cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial*. The Lancet Respiratory Medicine 2022 08 July 2022; Available from: https://www.sciencedirect.com/science/article/pii/S2213260022002156?via%3Dihub.
11. ESR. *COVID-19 Genomics Insights Dashboard (CGID) #21*. 2022 25 August 2022; Available from: http://esr2.cwp.govt.nz/assets/HEALTH-CONTENT/COVID-Genomics-Insights-Dashboard-CGID/CGID_no21_20220825.pdf.
12. de Ligt, J., et al. *COVID-19 Genomics Insight (CGI) Report. No.15, 13th July 2022, Unpublished ESR report.* 13 July 2022.

13. ESR. *COVID-19 Genomics Insights Dashboard (CGID) #20*. 2022 18 August 2022; Available from: https://www.esr.cri.nz/assets/HEALTH-CONTENT/COVID-Genomics-Insights-Dashboard-CGID/CGID_20_20220818.pdf.
14. Food and Drug Administration (FDA). *Frequently Asked Questions on the Emergency Use Authorization for Evusheld (tixagevimab co-packaged with cilgavimab) for Pre-exposure Prophylaxis (PrEP) of COVID-19*. 2022 29 June 2022]; Available from: https://www.fda.gov/media/154703/download.
15. Bruel, T., et al. *Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies*. Nature Medicine 2022 2022/06/01 [cited 28 6]; 1297-1302]. Available from: https://doi.org/10.1038/s41591-022-01792-5.
16. Aggarwal, A., et al. *SARS-CoV-2 Omicron BA.5: Evolving tropism and evasion of potent humoral responses and resistance to clinical immunotherapeutics relative to viral variants of concern*. medRxiv 2022; Available from: http://medrxiv.org/content/early/2022/07/10/2022.07.07.22277128.abstract.
17. Al Jurdi, A., et al. *Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave*. Am J Transplant 2022 Jun 21; 20220621:[Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.17128.
18. Kaminski, H., et al. *COVID-19 morbidity decreases with tixagevimab-cilgavimab preexposure prophylaxis in kidney transplant recipient nonresponders/low-vaccine responders*. Kidney Int 2022 Jul 20; 20220720:[Available from: https://pubmed.ncbi.nlm.nih.gov/35870641/.