

Introduction^{1, 2}

Tixagevimab plus cilgavimab (Evusheld[®]) injection is [provisionally registered](#) by the Therapeutic Goods Administration for use in Australia for:

- the prevention of COVID-19 in patients who are at risk of infection but have not been exposed to SARS-CoV-2 (pre-exposure prophylaxis)
- the treatment of COVID-19 in patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Use of tixagevimab plus cilgavimab is not an alternative or substitute for vaccination in individuals whom COVID-19 vaccination is recommended. **Vaccination is the preferred and primary option for the prevention of COVID-19.** Clinical trials for tixagevimab and cilgavimab were conducted when previous variants of SARS-CoV-2 were in circulation. Clinicians should consider the SARS-CoV-2 variant(s) being targeted and the possibility of reduced efficacy. Where possible, seek expert advice from Clinical Pharmacology and Infectious Diseases.

Patients who receive tixagevimab plus cilgavimab for pre-exposure prophylaxis should be informed of the potential for breakthrough infections to occur due to the development of viral variants that are resistant to the medicine. Patients should be instructed to promptly seek medical advice if signs or symptoms of COVID-19 occur.

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation. Additional resources to support the safe and effective use of tixagevimab and cilgavimab can be found [here](#).

Drug class and mechanism of action^{1, 2}

Tixagevimab and cilgavimab are IgG1 monoclonal antibodies that bind to distinct, non-overlapping epitopes within the receptor binding domain of the spike protein of the SARS-CoV-2 virus, thereby preventing the virus from infecting healthy cells. The monoclonal antibodies have been optimised with half-life extension and have been shown to offer protection lasting at least 6 months after a single intramuscular dose.

Approved indications^{1, 2}

Use of tixagevimab and cilgavimab in NSW must be in accordance with [ACI Guidance](#). The information below is derived from the Approved Product Information and **may differ from restrictions currently in place in NSW.**

For **pre-exposure prophylaxis** in adults and adolescents (aged 12 years and older and weighing at least 40 kg):

- who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments that make it likely that they will not mount an adequate immune response to COVID-19 vaccination (see ATAGI guidance* regarding immunocompromise) **OR**
- for whom vaccination with any approved COVID-19 vaccine is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

For **treatment** in adults with an active COVID-19 infection:

- who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- tixagevimab plus cilgavimab should be given as soon as possible after a positive viral test for SARS-CoV-2 and **within 7 days** after the onset of symptoms.

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In clinical trials, tixagevimab and cilgavimab was not administered to patients who had already received a COVID-19 vaccine.

*See ATAGI guidance on **immunocompromising therapies and conditions** (on Page 3 of [this document](#)) – note that this list is not exhaustive and clinicians may use their judgment for conditions or medications that are not listed, and which are associated with severe immunocompromise.

Contraindications and precautions^{1, 2}

- Known allergy to tixagevimab, cilgavimab or any of the excipients of this medicine (histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injection).
- Safety and efficacy of tixagevimab and cilgavimab in children < 18 years of age has not yet been established. *The recommended dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals 12 years of age and older and weighing at least 40 kg as observed in adults.*
- As with other medications given via the intramuscular route, tixagevimab and cilgavimab should be given with caution to patients with thrombocytopenia or any anticoagulation disorder.
- Consider the risks and benefits prior to using tixagevimab and cilgavimab in individuals at high risk for cardiovascular events. Advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of cardiovascular disease.
- See *Pregnancy and breastfeeding* section for recommendations in pregnancy and breastfeeding.

Pregnancy and breastfeeding^{2, 4}

Pregnancy

Tixagevimab and cilgavimab has been classified as **pregnancy category B2** by the TGA. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by treating health professionals.

Breastfeeding

There is no available data on the excretion of tixagevimab and cilgavimab in human milk, and the potential benefits and risks to a breastfed baby are not known. A decision regarding whether to discontinue breastfeeding or to abstain from tixagevimab and cilgavimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

Drug interactions²

No formal drug interaction studies have been conducted involving tixagevimab and cilgavimab. Tixagevimab and cilgavimab are not renally excreted or metabolised by the CYP450 enzymes. Texts such as [Liverpool COVID-19 Drug Interactions tool](#) and [Micromedex drug interactions tool](#) do not currently identify any drug interactions (as of 6 February 2023). Contact your local Pharmacy Department or medicines information service for further advice.

Presentations, storage and stability²

- Tixagevimab and cilgavimab will be supplied in individual vials in the same outer carton (packs). 2 packs are required to make up a dose for 1 patient. Each pack contains:
 - Tixagevimab 150 mg in 1.5 mL (100 mg/mL), **dark grey** vial cap.
 - Cilgavimab 150 mg in 1.5 mL (100 mg/mL), **white** vial cap.
- Store unopened vials at 2-8°C in original package. Protect from light. Do not freeze.
- The solutions for injection are preservative-free and therefore immediate administration of prepared syringes is advised. If immediate administration is not possible, the total time from vial puncture to administration **must not** exceed 4 hours (prepared syringes can be stored in fridge between 2-8°C or at room temperature up to 25°C).

Dose, timing and route of administration^{2, 3}

Recommended dose for **pre-exposure prophylaxis** is 300 mg tixagevimab and 300 mg cilgavimab.

- Administer as two separate, sequential **intramuscular injections**. Injections must be given in different injection sites, one in each of the gluteal muscles.
- No dose adjustments are required in renal or hepatic impairment.
- **Repeat doses may be administered once every 6 months at the discretion of the treating health care professional. Repeat dosing should only be considered if the treatment benefit outweighs the associated risks.**

Recommended dose for **treatment** is 300 mg tixagevimab and 300 mg cilgavimab.

- Administer as two separate, sequential **intramuscular injections**. Injections must be given in different injection sites, one in each of the gluteal muscles.
- No dose adjustments are required in renal or hepatic impairment.

Preparation and administration^{2, 3, 4}

Preparation
<p>The occupational hazard of intermittent low dose exposure to tixagevimab and cilgavimab is not known. To minimise exposure, gloves and surgical mask should be worn when preparing this medication. Please refer to local protocol or guidelines on this matter.</p> <ol style="list-style-type: none">1. Remove 2 vials of tixagevimab and 2 vials of cilgavimab from refrigerated storage. Do NOT shake the vials.2. Visually inspect each vial to ensure there is no damage to the vial or particulate matter/discolouration present. <i>Discard vials if solution is cloudy or discoloured (the solution should be clear to opalescent, colourless to slightly yellow).</i>3. Using aseptic technique:<ol style="list-style-type: none">a) withdraw 3 mL of tixagevimab from two vials into an appropriate syringe and label appropriately.b) withdraw 3 mL of cilgavimab from two vials into an appropriate syringe and label appropriately.
Administration
<p>Administer the prepared intramuscular injections consecutively, each at a different injection site (one in each gluteal muscle). Do not inject into skin that is tender, damaged, bruised, or scarred.</p>

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Monitoring requirements^{2, 4}

Monitor the patient for adverse effects after administration. Injection site reactions (pain, erythema, pruritus and induration) and hypersensitivity (including rash and urticaria) were seen in clinical trials.

Despite the drug sponsor and TGA not suggesting a post-administration observation period for tixagevimab and cilgavimab, **NSW Health recommends that patients are observed for 15 minutes after receiving their dose.**

Adverse effects^{2, 4}

- The most common adverse effects seen during clinical trials were headache (6%), fatigue (4%) and cough (3%). Additionally, a higher proportion of patients who received tixagevimab and cilgavimab compared to placebo in clinical trials had a serious cardiac adverse event or a thromboembolic serious adverse event. A causal relationship between tixagevimab and cilgavimab use and these events **has not** been established.
- As the proposed use is for a provisionally approved medicine which has no relevant post-marketing data, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use. Refer to [Product Information](#) for a complete list of possible adverse effects.

Reporting

- Tixagevimab and cilgavimab is subject to additional monitoring in Australia – this will allow rapid identification of new safety information. Healthcare professionals are asked to report any suspected adverse events to the [TGA](#), Astra Zeneca (drug sponsor) and via their facility's incident management system.
- Drug and Therapeutics Committee oversight in the access process will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. Tixagevimab and cilgavimab use and outcome reporting should occur as per local governance processes.

Changes made in version 1.3 – February 2023

- Amended based on update to TGA approved Product Information in December 2022 (provisional approval of treatment indication, amendment of dose for pre-exposure prophylaxis and addition of advice regarding repeat dosing).

References

1. Therapeutic Goods Administration. (2022). *TGA provisionally approves AstraZeneca's combination therapy (tixagevimab and cilgavimab, EVUSHELD) - for pre-exposure prevention (prophylaxis) of COVID-19*. Australian Government Department of Health. <https://www.tga.gov.au/tga-provisionally-approves-astrazenecas-combination-therapy-tixagevimab-and-cilgavimab-evusheld-pre-exposure-prevention-prophylaxis-covid-19>
2. Therapeutic Goods Administration. (2022). *Australian Product Information: EVUSHELD™ tixagevimab and cilgavimab*. Australian Government Department of Health. <https://www.tga.gov.au/sites/default/files/evusheld-pi.pdf>
3. Food and Drug Administration. (2023). *Factsheet for healthcare providers: Emergency Use Authorisation for EVUSHELD™ (tixagevimab co-packaged with cilgavimab)*. United States Government. <https://www.fda.gov/media/154701/download>
4. Therapeutic Goods Administration. (2022). *Consumer Medicine Information (CMI)*. Australian Government Department of Health. <https://www.tga.gov.au/sites/default/files/evusheld-cmi.pdf>

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