Tixagevimab + cilgavimab (Evusheld®) Prescribing Guideline - Adult

Last updated 28/11/2022

Background

Tixagevimab and cilgavimab (Evusheld®) has been granted provisional approval by the Therapeutic Goods Administration (TGA) for prophylaxis of COVID-19 in Australia. Evusheld® has a restricted listing on the Queensland Health Medicines Formulary. Please refer to the List of Approved Medicines (LAM) for details or if not listed, follow local processes for non-LAM approvals.

This guideline is based on the findings of clinical trials, recommendations from the National Clinical Evidence Taskforce (NCET)[1] the Evusheld® (tixagevimab + cilgavimab) product information[2] and consensus recommendations by the COVID Therapeutics Working Group (CTWG).

It is recommended this guideline is endorsed by local Medicines Management or Drug and Therapeutics Committees prior to use at your facility.

Mechanism of action

Evusheld® is a combination of 2 long-acting monoclonal antibodies, tixagevimab and cilgavimab, derived from the B-cells from donated plasma of patients previously infected with the SARS-CoV-2 virus.[2] Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of SARS-CoV-2, blocking its interaction with the human ACE-2 receptor. This prevents virus entry into cells, effectively neutralising the SARS-CoV-2 virus.

Indications

Refer to Decision Pathway and Guidance on the use of COVID-19 therapeutics for the treatment or prophylaxis of SARS-CoV-2.

- For detailed information on rationale for use please refer to the NCET
- For information on prescribing and eligibility in children please refer to CHQ-GDL-63327- The management and treatment of children with acute SARS-CoV-2 infection (COVID-19)
- For information on use in pregnancy and breastfeeding please refer to advice in the NCCET Guidelines and the product information for the individual COVID therapeutics as well as the in Guidance on the use of COVID-19 therapeutics for the treatment or prophylaxis of SARS-CoV-2

Tixagevimab and cilgavimab can be considered for prophylaxis and treatment of mild to moderate infection for adults and adolescents* over 12 years of age and weighing at least 40 kg, in the following scenarios:

Pre-exposure prophylaxis (PrEP)*:

- Eligibility for adults as per the criteria for immunosuppression listed in **Table 1**.
- Unable to be immunised due to genuine, severe allergy/contraindication **AND** not recently infected with SARS-CoV-2 within previous 3 months **AND** age ≥ 70 years **OR** age ≥ 50 years (**OR** ≥ 30 in those who identify as Aboriginal or Torres Strait Islander) with additional risk factors for severe disease

Table 1. Immunosuppression Criteria

Severe	Moderate
A patient is considered severely immunocompromised as per below: • B or T cell depleting therapy within previous 12 months (rituximab, ocrelizumab, obinutuzumab, ofatumumab, alemtuzumab) or planned to receive B or T cell depleting therapy within two weeks of tixagevimab and cilgavimab administration • High dose (> 1 g/m^2) cyclophosphamide within previous 12 months • Receiving Bruton's tyrosine kinase (BTK) inhibitors (zanubrutinib, ibrutinib, acalabrutinib) • Receiving JAK inhibitors, Sphingosine 1-phosphate receptor modulators , anti-complement antibodies and anti-thymocyte globulin (see decision pathway, page 3). • CAR-T/NK cell immunotherapy within previous 24 months • Stem cell transplant (SCT) – autologous SCT within previous 12 months, allogeneic SCT within previous 24 months, allogeneic SCT with chronic GvHD • Haematologic malignancy on active therapy • Non-haematological malignancy with current active treatment (e.g. chemotherapy, whole body irradiation) • Solid organ transplant on immunosuppressive therapy • HIV with CD4 cell count < 250 cells/mm^3 or unable to be established on effective antiretroviral therapy • Combined primary immunodeficiency syndromes (including SCID) • Common variable immunodeficiency (CVID) with additional T-cell defects, past opportunistic infection or requiring immunosuppressive therapy • Newly diagnosed humoral immunodeficiency with baseline IgG < 3 g/L	A patient is considered moderately immunocompromised as per below: • Primary immunodeficiency including combined immunodeficiency and syndromes, major antibody deficiency (e.g. common variable immune deficiency (CVID) or agammaglobulinemia), defects of innate immunity (including phagocytic cells), defects of immune regulation, complement deficiencies and phenocopies of primary immunodeficiencies. • Long term haemodialysis or peritoneal dialysis • Patients on immunosuppressive therapy listed in page 3 of the decision pathway, outside of severely immunosuppressed criteria **Patients who are moderately immunocompromised are less likely to derive clinical benefit from tixagevimab + cilgavimab (Evusheld®) unless they have other significant risk factors, or the patient has not seroconverted post vaccination**

Treatment^*

- as per Decision Pathway (adults)

* Approval to use of tixagevimab and cilgavimab in children and adolescents will be considered on a case-by-case basis after discussion with a specialist Paediatric Infectious Diseases physician. Please refer to CHQ-GDL-63327- The management and treatment of children with acute SARS-CoV-2 infection (COVID-19)

^ Treatment with Evusheld® for mild to moderate disease should commence within 5 days of symptom onset and for severe disease should be initiated within 12 days of symptom onset in adults.

For information on Patient Consent please refer to advice in Guidance on the use of COVID-19 therapeutics for the treatment or prophylaxis of SARS-CoV-2.

Contraindications and Precautions[2]

- Individuals with a history of severe hypersensitivity (including anaphylaxis) to tixagevimab or cilgavimab or to any of the excipients.
    - Excipients for Evusheld®: histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injection
- Hypersensitivity including anaphylaxis are rare with IgG 1 monoclonal antibodies. Discontinue if signs and symptoms of severe hypersensitivity reaction or anaphylaxis occurs and initiate appropriate medicinal products and /or supportive therapy.
- Clinically significant bleeding disorders
- Cardiovascular and thromboembolic events

Please also refer to the Evusheld® product information for further details regarding special warnings and precautions for use.

Drug interactions

Interaction studies have not been conducted with Evusheld® active ingredients or excipients. Evusheld® is not expected to undergo hepatic enzyme or renal elimination.

For the most up to date interactions, check the Liverpool COVID-19 Drug Interactions Checker, product information or Micromedex for advice on specific drugs.

Dosing and Administration

For patients receiving tixagevimab and cilgavimab that do not have an active COVID-19 infection, so administration may occur outside COVID-specific facilities, e.g. using existing administration locations for chemotherapy or biologic immunosuppressants. Administration of tixagevimab and cilgavimab should occur in setting with access to facilities to manage anaphylaxis.

Tixagevimab and cilgavimab is given by deep intramuscular injection.[2] Caution is advised with this route of administration in patients with a history of neutropenia or thrombocytopaenia or who are anticoagulated. Local procedures should be followed, and haematology consulted if necessary.

Tixagevimab and cilgavimab is administered via intramuscular (IM) injection:

Table 2. Tixagevimab-cilgavimab (Evusheld®) dosage recommendation table

Indication	Route	Dosage
PrEP	Intramuscular	Two separate sequential injections: 150mg/1.5mL of tixagevimab and 150mg/1.5mL of cilgavimab = a total dose of 300mg of Evusheld®
Treatment* (off-label) Mild-moderate	Intramuscular	NOT received a PrEP dose of Evusheld® in the previous 6 months: • Two separate sequential injections: 300mg (=3mL) of tixagevimab and 300mg (=3mL) of cilgavimab. = a total dose of 600 mg of Evusheld® OR if discomfort due to injection is a concern • as four separate sequential injections of 150mg/1.5mL of tixagevimab and 150mg/1.5mL = a total dose of 600 mg of Evusheld® Received a PrEP dose of Evusheld® in the previous 6 months, consider an additional dose of 150mg of tixagevimab and 150 mg cilgavimab: • Two separate sequential injections: 150mg/1.5mL of tixagevimab and 150mg/1.5mL of cilgavimab = a total dose of 300mg of Evusheld®
Treatment* (off-label) Severe	Intravenous	NOT received a PrEP dose of Evusheld® in the previous 6 months: 300mg (=3mL) of tixagevimab and 300mg (=3mL) of cilgavimab (total dose =600 mg of Evusheld®) in 250mL of Sodium Chloride 0.9% over 30 mins

* Treatment is currently off-label use in Australia

The **total dose of Evusheld®** received by a patient **must not exceed 600 mg (tixagevimab 300 mg and cilgavimab 300 mg) in 6 months.**

Do not shake the vials.

Tixagevimab and cilgavimab should be administered at different injection sites, one in each of the gluteal muscles. Tixagevimab and cilgavimab has only been studied as a single dose; neither safety nor efficacy data are available for repeat dosing.

The duration of protection following administration of a single 300 mg dose is estimated to be at least 6 months. Repeat dosing for prophylaxis or treatment can be considered after 6 months from the most recent dose in those that are severely immunocompromised but this is currently off-label use in Australia.[1,3]

Patients should be observed for 15 minutes after administration of their dose.[4]

Intravenous administration is an off- licensed method of administration and may be considered in those at high risk of bleeding (e.g. thrombocytopenia or other coagulation disorders) or reduced muscle mass. Studies in adults have used 300 mg (tixagevimab 150 mg - cilgavimab 150 mg) and 600mg (i.e. 300mg of each component) as intravenous infusion in 100-250 mL of sodium chloride 0.9% over 15 or 30 minute infusion respectively.[5,6]

Tixagevimab and cilgavimab is not recommended as a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

Despite very limited data in these populations, based on drug pharmacokinetics, no dose adjustments are required in elderly patients or those with liver or kidney impairment (including dialysis).[2,3]

Adverse events[2]

Evusheld® is currently provisionally approved by the TGA and any adverse events should be reported to the TGA (www.tga.gov.au/reporting-problems) and via local event reporting processes (e.g. Riskman). Some of the reported adverse events are:

- Hypersensitivity – including rash and urticaria
- Injection site reaction
- Dizziness
- Headache
- Fatigue
- Cardiovascular effects (e.g. cardiomyopathy, heart failure, cardiomegaly, myocardial infarction)

For a comprehensive list and further details of adverse events see product information.

Prescription and Governance

Tixagevimab and cilgavimab (Evusheld®) has a restricted listing on the Queensland Health Medicines Formulary (List of Approved Medicines): *'On the advice of a specialist physician for use in COVID-19 in accordance with recommendations in the State-wide COVID-19 Treatment Guideline and the tixagevimab + cilgavimab prescribing guideline'*. Individual governance of tixagevimab and cilgavimab prescribing should be managed by a lead clinician in each Hospital and Health Service

Authorised prescribers

Eligible prescribers are those that have an affiliation with a hospital e.g. Hospital Medical Specialists and their respective registrars, residents OR a GP affiliated with hospital. Prescribers are required to complete a Request to Access Form for each patient, confirming patient suitability and consent to treatment plus a prescription.

Access and Supply

Access to tixagevimab and cilgavimab is regulated by the National Medical Stockpile and is currently available through public and private hospital pharmacies. Australia has received a small initial quantity of tixagevimab and cilgavimab, from which Queensland has been allocated a limited number of doses for use in public and private hospital settings. To ensure equity of access across Queensland, tixagevimab and cilgavimab has been triaged to those at the highest risk of severe COVID-19 outcomes who are likely to derive the most benefit. The CTWG has based these recommendations on the consensus of an expert group of lead clinicians. Completion of the Request to Access Form is a requirement for supply.

QH facilities: use the MARP portal Login - Medication Access Request Portal (health.qld.gov.au) OR download the application from Software Centre for the various Evusheld® forms

For Private facilities: use the following link Clinical guidelines | Queensland Health and send completed forms to CTWG@health.qld.gov.au

Anti-spike IgG serology testing should be performed where feasible prior to administration of tixagevimab and cilgavimab. There is no requirement to delay administration pending serology results.

Patients who have previously had COVID-19 infection

After COVID-19 infection has resolved, patients may be considered for prophylaxis on the basis of immunosuppressive status and immunity to COVID-19. Consider serology testing to assess immunity. There are currently no data to guide whether administration should be delayed after other monoclonal antibody use (i.e. sotrovimab).

In patients whom tixagevimab and cilgavimab was administered for treatment of COVID-19 infection, refer to the Australian Technical Advisory Group on Immunisation (ATAGI) for vaccination recommendations.

Vaccination

For patients recently administered tixagevimab and cilgavimab, COVID-19 vaccination can be given at any time.

For patients recently administered a COVID-19 vaccine, it is recommended to wait 2 weeks after vaccination before receiving tixagevimab and cilgavimab.[3,7]

Monitoring

The use of tixagevimab and cilgavimab supplied from the National Medical Stockpile requires reporting of clinical outcomes to the National Medical Stockpile Taskforce. Prescribers agree to these terms when completing a tixagevimab and cilgavimab Request to Access Form. Data required includes eligibility, confirmation of dose delivered and outcome: recovery, ICU or death and anti-spike IgG serology testing—see 'Access and supply' for location of outcome and serology forms.

Storage and Stability

Please refer to the Evusheld® product information for advice on storage and stability.[2]

Prescribing and Ordering

Refer to Appendix 1 for examples of ieMR(R) and National Inpatient Medication Chart (non-ieMR(R) ordering.

References

1. National COVID-19 Clinical Evidence Taskforce: Australian guidelines for the clinical care of people with COVID-19. 2021. [cited 2022 October 4]. Available from: https://covid19evidence.net.au/#living-guidelines
2. AstraZeneca (Australia) Pty Ltd. Australian product information – Evusheld® (tixagevimab and cilgavimab). 2022. Published 2022 February 26.
3. US Food and Drug Administration. Fact sheet for health care providers: Emergency Use Authorization for Evusheld (tixagevimab co-packaged with cilgavimab). Revised 06/2022 https://www.fda.gov/media/154701/download .[Accessed 26/7/2022]
4. NSW Therapeutic Advisory Group Inc and the Clinical Excellence Commission. Drug Guideline: use of tixagevimab and cilgavimab injection for COVID-19 v1.4 updated March 2022. NSW Department of Health.
5. ACTIV-2 /A5401. Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID). A Multicentre Trial of the AIDS Clinical Trials Group (ACTG). Final version 7.0 June 29/2021. https://www.fnih.org/sites/default/files/2021-10/ACTIV-2_v7.0-wLOA%20073021.pdf
6. 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 trail. Lancet Resp Med 2022; S2213-2600(22)00215-6.doi: 10.1016/S2213-2600(22)00215-6.
7. Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19. JAMA. 2022;327(4):384-5.

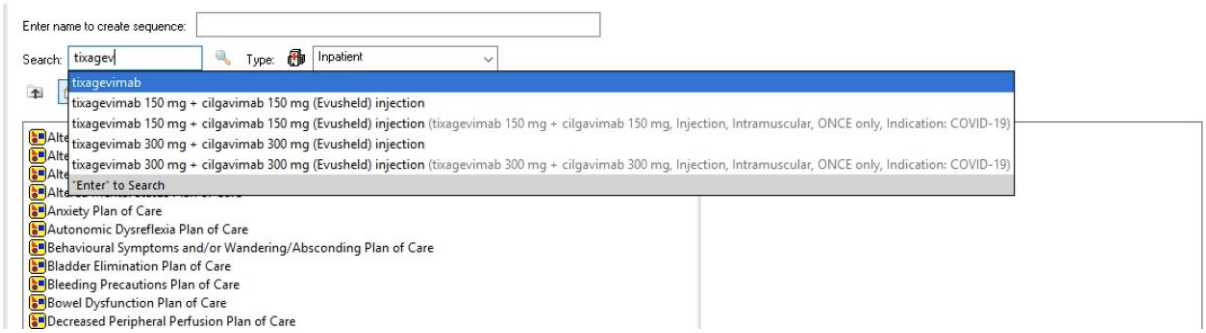
Appendix 1

Ordering in the ieMR®

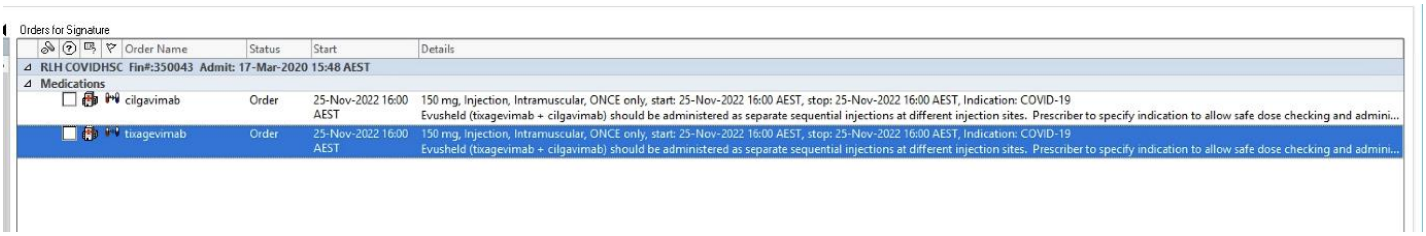
Tixagevimab and cilgavimab are ordered as a single combined therapy however, to allow each injection to be signed off as administered, they will drop into the MAR as separate orders.

Prophylaxis Dosing:

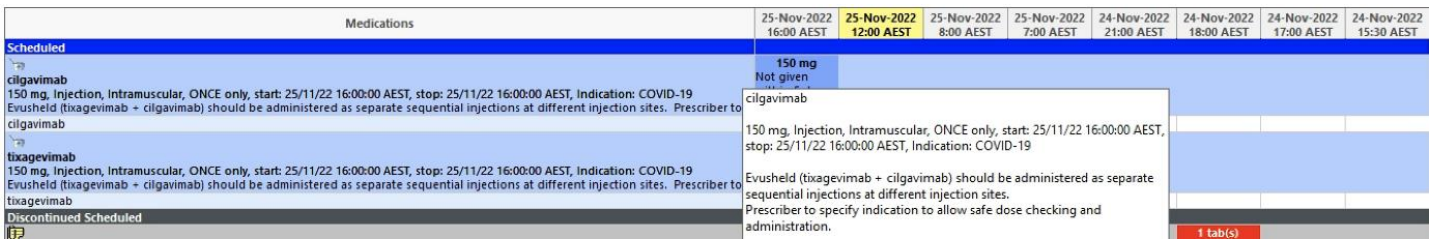
- **In the Orders window (150mg+150mg):**



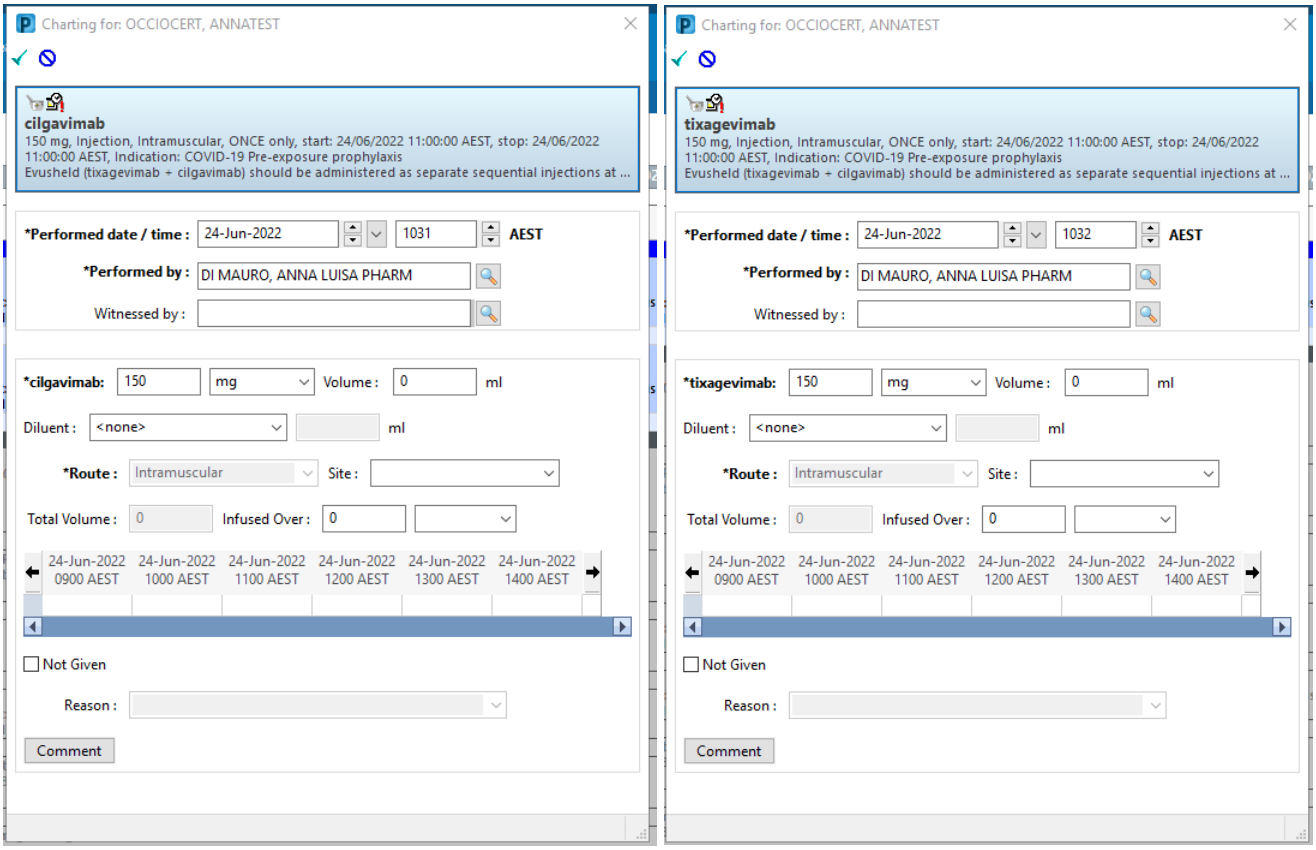
- **Orders appear separately on the scratchpad**:



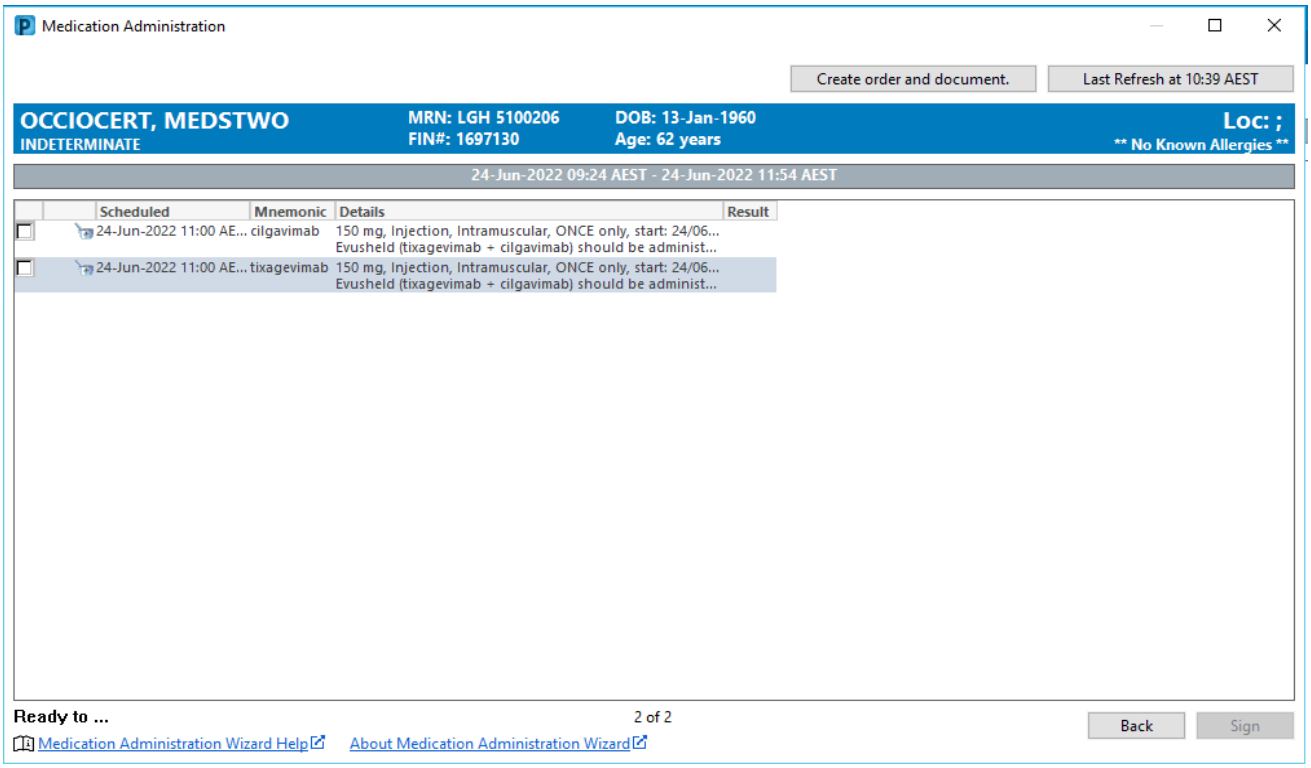
- **Orders on the MAR** – note that orders on the MAR are listed alphabetically and if there are other orders, they may not appear together.



- **MAR administration window**

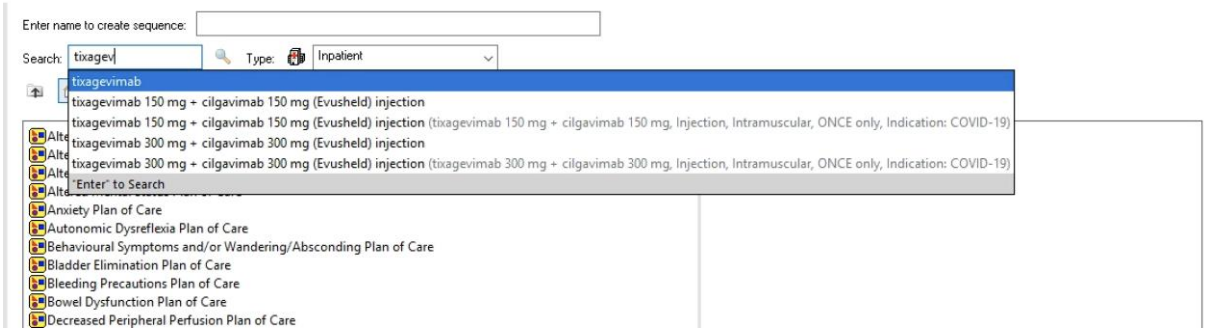


- **MAW window**

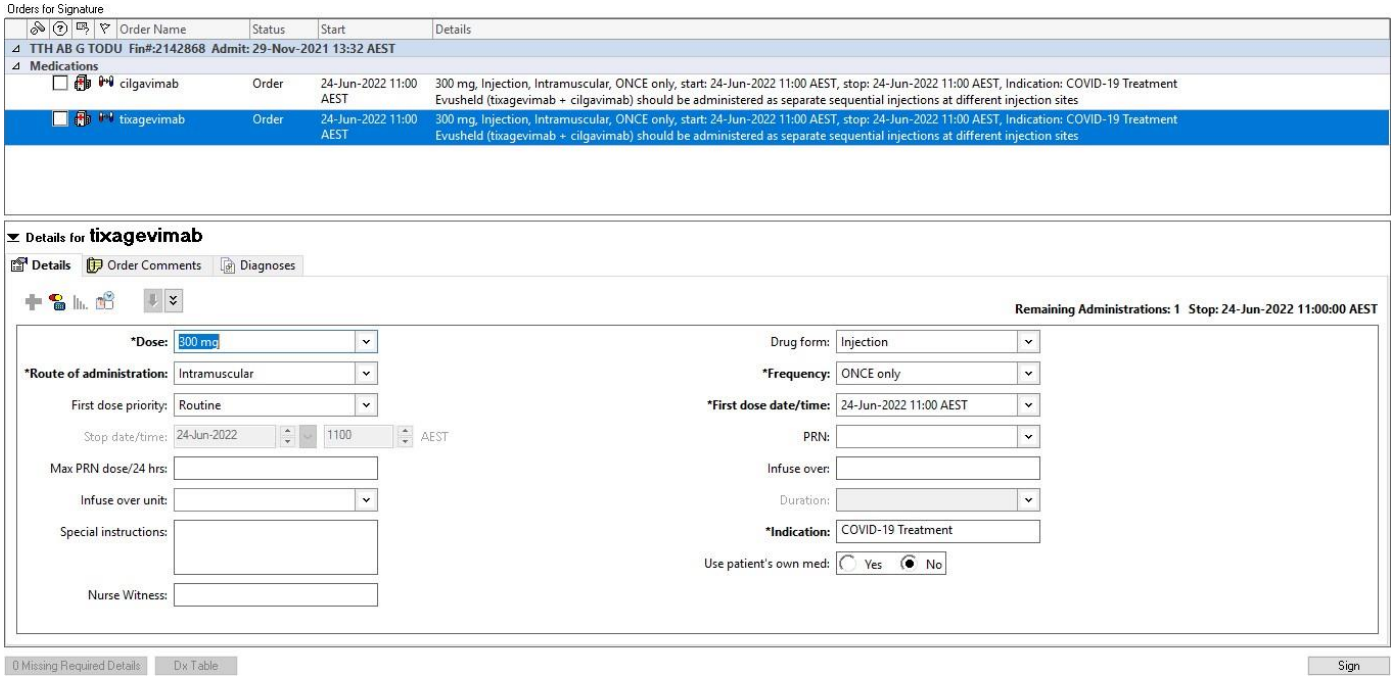


Treatment Dosing:

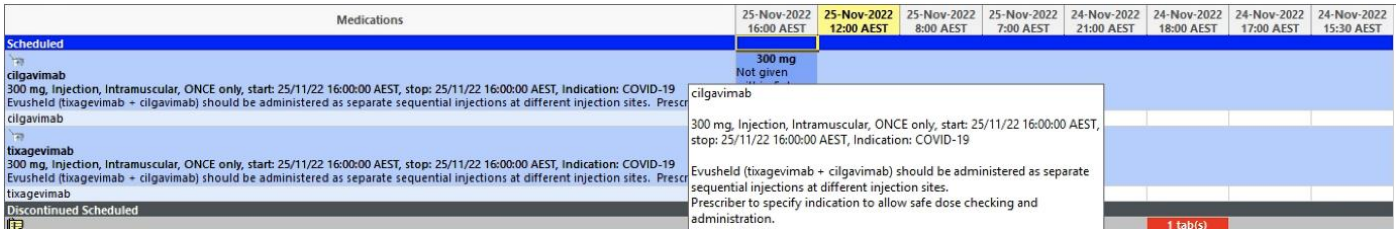
- **In the Orders window (300mg + 300mg):**



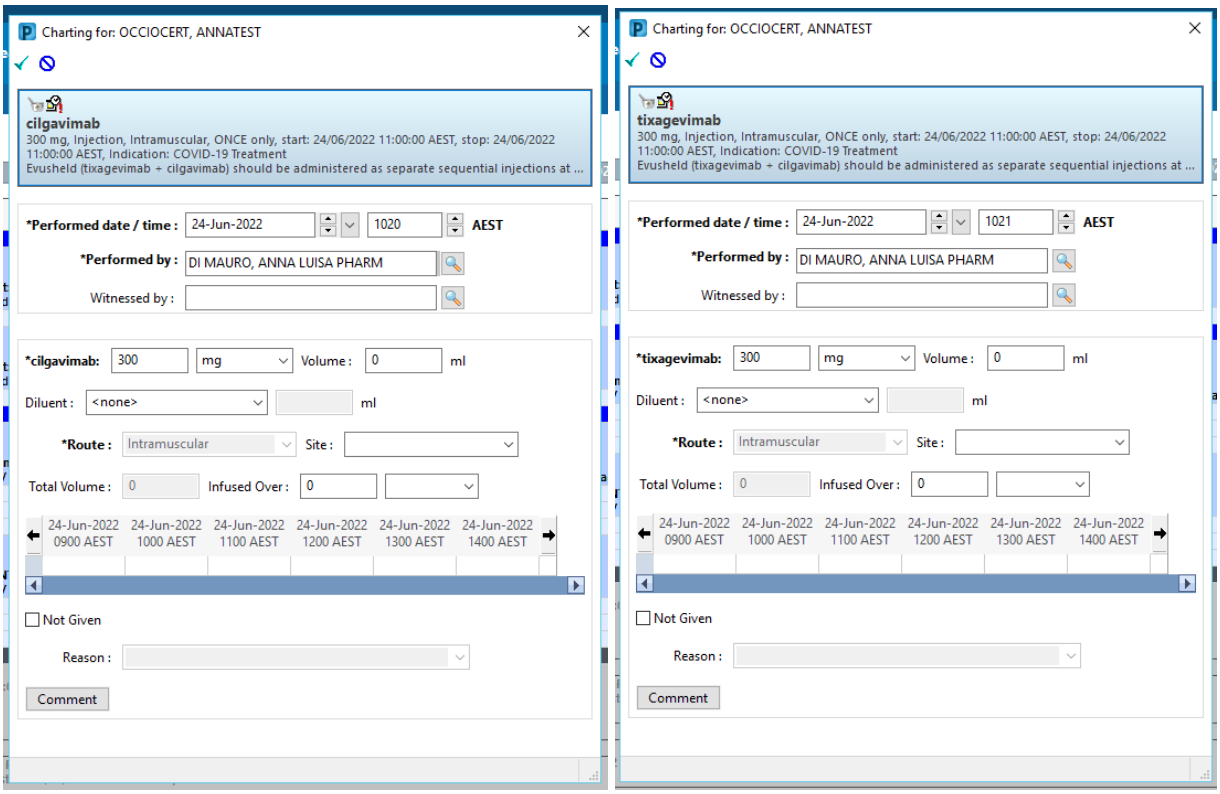
- **Orders appear separately on the scratchpad**:



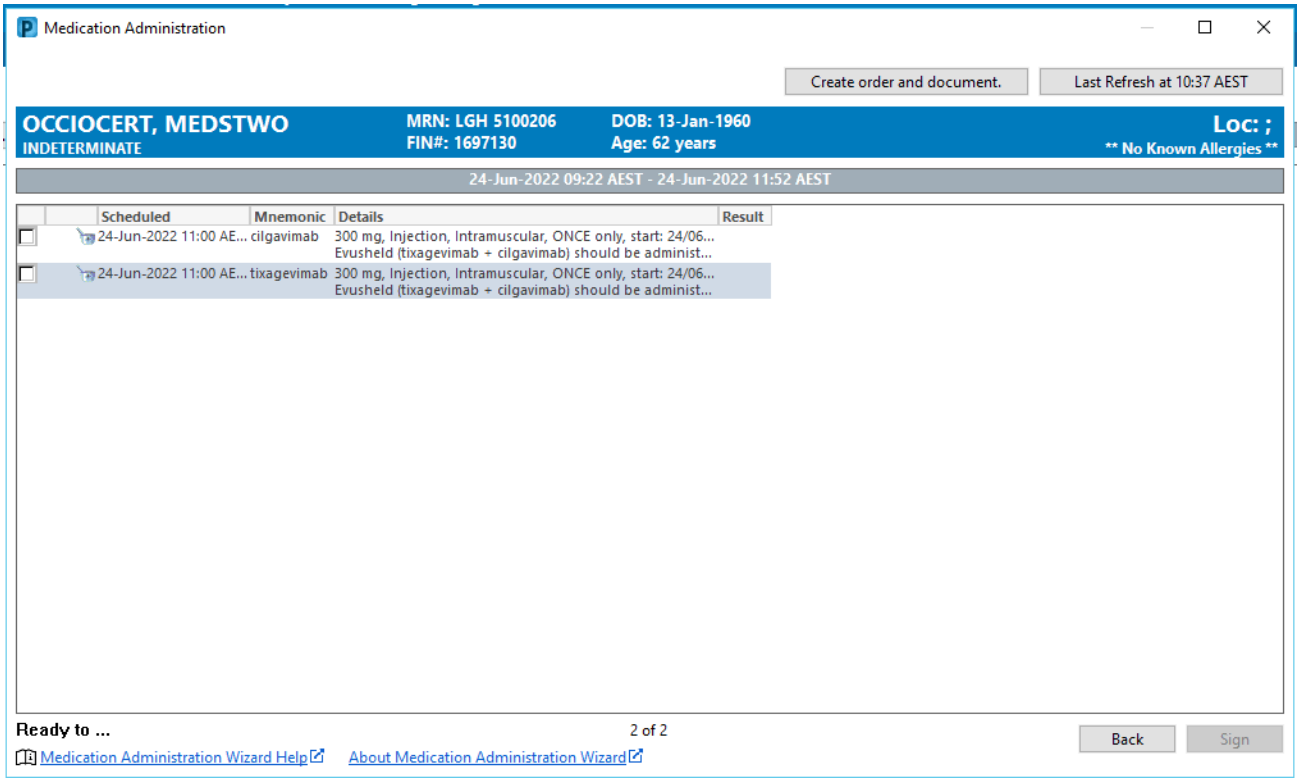
- **Orders on the MAR** – note that orders on the MAR are listed alphabetically and if there are other orders, they may not appear together.



- **MAR administration window**



- **MAW window**



National Inpatient Medication Chart (NIMC) - Non ieMR® ordering

Prescribing on the National Standard Medication Chart (NSMC) is provided in Image 1 (prophylaxis or top-up dose) and 2 (treatment dose)

Image 1**.** Prescribing of tixagevimab and cilgavimab for prophylaxis or top up dose

Government

Facility / Service: RBWH

Year: 2022 Ward / Unit: WATT

MEDICATION CHART 1 of 1

ADDITIONAL CHARTS

☑ IV Fluid ☐ BGL / Insulin ☐ Acute Pain ☐ Clozapine

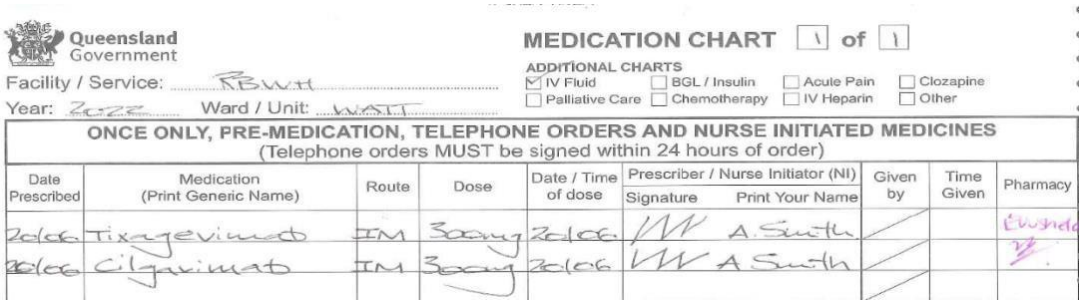
☐ Palliative Care ☐ Chemotherapy ☐ IV Heparin ☐ Other

ONCE ONLY, PRE-MEDICATION, TELEPHONE ORDERS AND NURSE INITIATED MEDICINES

(Telephone orders MUST be signed within 24 hours of order)

Date Prescribed	Medication (Print Generic Name)	Route	Dose	Date / Time of dose	Prescriber / Nurse Initiator (NI) Signature	Prescriber / Nurse Initiator (NI) Print Your Name	Given by	Time Given	Pharmacy
29-3	Tixagevimab	IM	150mg	29-3-22		Amy Ligh			(Evusheld)
29-3	Cilgavimab	IM	150mg	29-3-22		Amy Ligh			OR

Image 2**.** Prescribing of tixagevimab and cilgavimab for treatment



Queensland Government

Facility / Service: RBWH

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MEDICATION CHART 1 of 1

ADDITIONAL CHARTS

☑ IV Fluid ☐ BGL / Insulin ☐ Acute Pain ☐ Clozapine

☐ Palliative Care ☐ Chemotherapy ☐ IV Heparin ☐ Other

ONCE ONLY, PRE-MEDICATION, TELEPHONE ORDERS AND NURSE INITIATED MEDICINES

(Telephone orders MUST be signed within 24 hours of order)

Date Prescribed	Medication (Print Generic Name)	Route	Dose	Date / Time of dose	Prescriber / Nurse Initiator (NI) Signature	Prescriber / Nurse Initiator (NI) Print Your Name	Given by	Time Given	Pharmacy
2/1/06	Tixagevimab	IM	300mg	2/1/06		A Smith			Evusheld
2/1/06	Cilgavimab	IM	300mg	2/1/06		A Smith			

Version	Amendments	Author/s	Approved for Publication
1.0	New document	Panteha Voussoughi Ashlea McCarron Dr Andrew Henderson	Approved by: Prof. Keith McNeil, Chief Medical Officer, Queensland Health 27/10/2022
1.1	Minor updates: - Change terminology from NCCET to NCET - Clarification of prophylaxis eligibility and addition of immunosuppression table from decision pathway	Ashlea McCarron	CTWG Chair 28/11/2022