INTERIM GUIDELINES FOR EVULSHELD AS PRE-EXPOSURE PROPHYLAXIS IN COVID-19

Interim guideline updates 03/11/2022

This interim guideline has updated the dosing required for Evusheld as pre-exposure prophylaxis. Please see section 3 of this document.

The new recommended dosage regimen is a 600 mg intramuscular (IM) dose (300 mg each of tixagevimab and cilgavimab) administered as two separate IM injections. This update is based on the latest information available and modelling assessments against BA.2, BA.4 and BA.5 Omicron strain based on neutralization activity.

1. Background

Tixagevimab and cilgavimab (Evusheld™) are Long-acting dual monoclonal antibodies that target SARS-Cov-2 spike proteins and blocks viral attachment and entry into cells. The primary data supporting the Evusheld EUA are from the ongoing PROVENT Phase III pre-exposure prevention trial, which showed a statistically significant reduction (77% at primary analysis, 83% at median six-month analysis) in the risk of developing symptomatic COVID-19 compared to placebo, with protection from the virus continuing for at least six months[1]. Data till date supports the use of Evusheld against the emerging omicron variants. New preclinical authentic 'live' virus data from Washington University School of Medicine demonstrated that Evusheld retains potent neutralising activity against the emerging and highly transmissible Omicron SARS-CoV-2 BA.2 subvariant.[2] The data also showed that Evusheld retains activity against Omicron BA.1 and BA.1.1. This is subject to change as more evidence is published in the future.
Pre-exposure prophylaxis with Evusheld 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.

Evusheld is currently been approved as pre-exposure prophylaxis drugs for COVID-19 only by NPRA, Malaysia and not for post exposure prophylaxis or treatment of confirmed cases.

2. Clinical criteria for pre-exposure prophylaxis

Evusheld can be used as pre- exposure prophylaxis of COVID-19 Infection among adults and pediatric patients who are:

- 12 years of age or older
  AND
- Weighing at least 40 kg
  AND
- Who are currently not infected with SARS-COV-2 and have not had a recent exposure to an individual infected with SARS-COV-2
  AND
- Moderately to severely immunocompromised and may have inadequate immune response to COVID -19 vaccination, or are not able to be fully vaccinated with any available COVID-19 vaccines due to a severe adverse reaction to a COVID-19 vaccines or any of its components.

3. Categories of patients for access to Evusheld

These group of patients (Table 1) are to be **prioritized** in descending order to receive Evusheld

Table 1: Priority group 1 to receive Evusheld

1. Bone marrow transplant patients on immunosuppressive therapy
2. Solid Organ transplant patients on immunosuppressive therapy
3. Haematological malignancies on active chemotherapy
4. Non-haematological malignancies on active chemotherapy

Once Evusheld is more readily available, then the group below (Table 2) **can be considered** in the descending order of priority.

Table 2: Priority Group 2 to receive Evusheld

1. Patient who are within a year of receiving B cell depleting therapies e.g. Rituximab, ocrelizumab, ofatumumab, alemtuzumab
2. Patient with severe combined immunodeficiency
3. Patients with untreated HIV with CD4 T lymphocyte count < 50 cells/ mm

4. Unvaccinated due to medical reasons with age more than 60
5. Unvaccinated due to medical reasons with age less than 60 with comorbid

- This list is not exhaustive of all the immunocompromised, clinicians may use their judgement for conditions or medications that are not listed and which are associated with severe immunocompromised state.

4. Dosing and administration of Evusheld

a. Tixagevimab 300 mg plus Cilgavimab 300 mg (Evusheld) is administered as 2 separate consecutive IM injections at different sites, preferably one in each of the gluteal muscles.

Evusheld* (Tixagevimab 150mg/1.5ml Cilgavimab 150mg/1.5ml)	Antibody dose	Number of vials needed	Volume to withdraw from each vial
	300mg	2 vials	1.5ml (Total volume is 3 ml)
	300mg	2 vials	1.5ml (Total volume is 3 ml)

* Each contain 1.5ml as a single dose vial.

b. A second dose should be given as soon as possible for individuals that have received Tixagevimab 150 mg plus Cilgavimab 150 mg (Evusheld) in following conditions:

i. If initial dose was administered <u>less than 3 months ago</u>, the second dose should be Tixagevimab 150 mg plus Cilgavimab 150 mg (Evusheld)

ii. If the initial dose was administered <u>more than 3 months ago</u>, the second dose should be Tixagevimab 300 plus Cilgavimab 300 mg (Evusheld)

Timing of the initial dose	To add on 2nd dose
<u>≤</u> 3 months ago	Tixagevimab 150 mg plus Cilgavimab 150 mg (Evusheld)
> 3 months ago	Tixagevimab 300 mg plus Cilgavimab 300 mg (Evusheld)

No dosage adjustment required in pregnant or lactating individuals, in geriatrics, and in individuals with renal impairment

There are no safety and efficacy data available with repeat dosing at present moment.

5. Temporary deferral

Timing and temporary deferral of pre- exposure prophylaxis should be considered in the following conditions:

1. Two (2) weeks after COVID-19 vaccination
2. Recipient of monoclonal antibody within 3 months
3. In any evidence of acute infection; including COVID-19 infection that has not resolved

Clinicians may use their judgment on other conditions not listed.

6. Use in special population

a. Pregnancy: Evusheld should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus
b. Lactation: Unknown data
c. Patients on dialysis: dialysis is not expected to impact the PK of Evusheld
d. Liver impairment: No data available
e. Less than 12 years old or weighing less than 40 kg: Safety and efficacy use in paediatrics population have not been evaluated and individuals with similar body weight have been included in the trials

7. Warning and Precautions

a. Serious hypersensitivity reactions including anaphylaxis, have been observed with Evusheld.

Dyspnoea	Chills
Tachycardia	Fatigue, Myalgia
Chest Pain or discomfort	Dizziness
Nausea and vomiting	Urticaria
Angioedema, Pruritus	Wheezing
Flushing	Vasovagal reactions
Hyperhydrosis	Throat irritation

b. Clinically Significant Bleeding Disorders

As with any other intramuscular injection, Evusheld should be given with caution to individuals with thrombocytopenia or any coagulation disorder.

c. There is a risk of cross-hypersensitivity with COVID-19 vaccines as Evusheld contains polysorbate 80, which is in some COVID-19 vaccines is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines.

d. Known allergy to tixagevimab, cilgavimab or any of the excipients of this medicine (histidine, histidine monohydrochloride monohydrate, sucrose, water for injection).

e. Cautious use on high-risk individuals at risk of cardiovascular events as in the PROVENT trial there was a higher rate of cardiovascular adverse events including myocardial infarction and cardiac failure but however a temporal relationship was never found. Consider the Risk versus Benefit in these individuals and advise them to seek immediate attention if they experience signs and symptoms of heart disease.

8. Adverse reactions

Most common: headache (6%), fatigue (4%) and cough (3%)

9. Drug interaction

No formal drug interaction studies have been conducted involving Evusheld. Evusheld is not renally excreted or metabolised by the CYP450 enzymes.

10. COVID-19 testing

Saliva or Nasopharyngeal RTK test would be sufficient as a pre-requisite screening in symptomatic patients but not required in asymptomatic patients. The decision to do the test will depend on the clinical judgement of the attending physician. Use of SARS-COV-2 PCR is case to case basis and not routinely recommended especially in asymptomatic individuals.

11. Administration

a. Place of administration and monitoring of the condition of patients should be in a hospital setting. The details to be decided locally
b. Administered by a qualified healthcare provider with appropriate medical support to manage severe hypersensitivity reactions or anaphylaxis.
c. Administer the two components of Evusheld consecutively.
d. Administer the IM injections at different injection sites, preferably one in each of the gluteal muscles, one after the other.

e. Clinically monitor individuals after injections and observe for at least 1 hour
f. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur while taking Evusheld, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Note: Evusheld must be stored in cold chain.

References

1. Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19. N Engl J Med 2022; 386:2188-2200
2. FDA fact sheet - EVUSHELD
3. Case, J et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains
4. NSW therapeutic advisory group guideline
5. Victoria Department of Health
6. NIH treatment guidelines prevention of SARS-COV-2