Evusheld

Evusheld (tixagevimab/cilgavimab) is a long-acting monoclonal antibody available under EUA by the FDA for COVID-19 pre-exposure prophylaxis (PrEP) in certain high-risk, immunocompromised individuals and those unable to receive the COVID-19 vaccine because of a previous severe reaction.

Evusheld Prescribing

1) Per the FDA EUA, Evusheld may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under Michigan law to prescribe drugs in the therapeutic class to which Evusheld belong (monoclonal antibodies). See full applicable Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on alternatives.
2) The dosage of EVUSHELD for emergency use is:
    - Initial dose: 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections.
3) ***Repeat dose:*** The SARS-CoV-2 variants that will be circulating in the U.S. when Evusheld may need to be redosed are not known at this time and therefore repeat dosing recommendations cannot be made; the Fact Sheets will be revised with repeat dosing recommendations in the future when more data are available.
4) Evusheld may be given to individuals >12 years old and weighing at least 40kg who are not currently infected with COVID-19, have not had a known exposure to someone with SARS-CoV-2 and:
    - May NOT mount an adequate immune response to COVID-19 vaccination.
    - May not be eligible for COVID-19 vaccination due to a history of severe adverse reaction (severe allergic reaction) to either the COVID-19 vaccine, or the COVID-19 vaccine components.
    - Have moderate to severe immune compromise related to a medical condition or receipt of immunosuppressive medications or treatments.
    - Evusheld PrEP is not a substitute for vaccination.

Operationalizing the Administration of Evusheld

Because health care organizations are unique, operationalizing access to Evusheld may be done in different ways within the health care system. This is a formative process that will need to be adapted and revised over time to best serve high-risk patients. Health care systems should consider the following, in consultation with their scarce resource allocation committees, when establishing policies for Evusheld administration to qualifying patients.

Identify and Screen Potentially Eligible Patients

- Health care providers and health systems should work to identify their patient population eligible to receive Evusheld.
- Patient screening should be done to determine eligibility for Evusheld. This can be accomplished through an electronic medical record search for appropriate conditions (ICD-10 codes)
- Pharmacy identification of patients currently receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab).
- Outreach to clinics and specialty physician offices asking them to identify patients who meet the eligibility criteria (rheumatology, oncology, hematology, transplant services).
- Using a list of identified and screened patients, those meeting the criteria should be placed in the order to receive Evusheld.
- After identifying patients who have opted to receive Evusheld, a qualified health care provider or designee should contact each patient and:
    - Provide counseling on the potential risks and benefits of Evusheld and provide a copy of the Fact Sheet for Patients and Caregivers.
    - Provide instructions for scheduling and administration.

Administering and Monitoring Evusheld

- Once patients have been selected and agree to receive Evusheld, an order will be provided by an authorized healthcare provider. The medication should be provided to the site of administration and an appointment should be scheduled.
- Evusheld is administered as directed by the FDA fact sheet for healthcare providers.
- Patients must be observed for at least 60 minutes following administration.
- The current EUA calls for the re-administration of Evusheld every six months to sustain pre- exposure prophylaxis. However, it is unknown what SARS-CoV-2 variants that will be circulating in the United States when Evusheld may need to be redosed are not known at this time and therefore repeat dosing recommendations cannot be made; the Fact Sheets will be revised with repeat dosing recommendations in the future when more data are available.
- Health care systems should monitor patients receiving Evusheld for safety and effectiveness in preventing COVID-19 infections, especially hospitalizations or deaths.

Evusheld Warnings and Precautions

Hypersensitivity Including Anaphylaxis

- Serious hypersensitivity reactions, including anaphylaxis, have been observed with Human immunoglobulin G1 (IgG1) monoclonal antibodies like Evusheld. 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. Clinically monitor individuals after injections and observe for at least one hour.

Clinically Significant Bleeding Disorders

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

Cardiovascular Events

- In PROVENT (LB5. PROVENT: Phase 3 Study of Efficacy and Safety of AZD7442 (Tixagevimab/Cilgavimab) for Pre-exposure Prophylaxis of COVID-19 in Adults (nih.gov) there was a higher rate of cardiovascular serious adverse events (SAEs), including myocardial infarction (one fatal SAE) and cardiac failure, in subjects who received Evusheld compared to placebo. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern.
- A causal relationship between EVUSHELD and these events has not been established. There was no signal for cardiac toxicity or thrombotic events identified in the nonclinical studies. Consider the risks and benefits prior to initiating Evusheld in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event.

Drug Interaction

Drug-drug interaction studies have not been performed. Tixagevimab and cilgavimab are not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

Use in Specific Populations

Pregnancy

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. Nonclinical reproductive toxicity studies have not been conducted with tixagevimab and cilgavimab. In a tissue cross-reactivity study assessing off-target binding of tixagevimab and cilgavimab to human fetal tissues no binding of clinical concern was observed. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, tixagevimab and cilgavimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of tixagevimab and cilgavimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Lactation

There are no available data on the presence of tixagevimab or cilgavimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evusheld and any potential adverse effects on the breastfed infant from EVUSHELD.

Pediatric Use

EVUSHELD is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of EVUSHELD have not been established in pediatric individuals. The 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, since adults with similar body weight have been included in the trials PROVENT and STORM CHASER Phase III Double-blind, Placebo-controlled Study of AZD7442 for Post- Exposure Prophylaxis of COVID-19 in Adults - Full Text View - ClinicalTrials.gov

Geriatric Use

Of the 2,029 subjects in the pooled pharmacokinetics (PK) analysis (Phase I and Phase III studies), 23% (N= 461) were 65 years of age or older and 3.3% (N= 67) were 75 years of age or older. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger subjects.

Renal Impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine, renal impairment is not expected to affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

Hepatic Impairment

The effect of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

Other Specific Populations

Based on a population PK analysis, the PK profile of tixagevimab and cilgavimab was not affected by sex, age, race, or ethnicity. Population PK model-based simulations suggest that body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in healthy adults over the range of 36 kg to 177 kg.