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Subject: High-risk cardiac patients and the use of EVUSHELD (tixagevimab co-packaged with cilgavimab).

Dear Healthcare Professional,

AstraZeneca GCC in agreement with Saudi Food and Drug Agency (SFDA) would like to notify you of the important safety information for EVUSHELD (tixagevimab with cilgavimab):

Summary

- In a Phase III clinical study evaluating EVUSHELD for prophylaxis (PROVENT) against COVID-19, a small numerical imbalance in cardiovascular serious adverse events (SAEs) was observed between the EVUSHELD and placebo groups.
- A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction SAEs, one of which resulted in death.
- All participants who experienced these events 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.
- Healthcare professionals should 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.

Background on the safety concern

SFDA has issued an Emergency Use Authorisation (EUA) in the Kingdom of Saudi Arabia for the use of EVUSHELD for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals: (12 years of age and older weighing at least 40 kg).

The data supporting this EUA are based on analyses from the Phase III trials PROVENT (NCT04625725) and STORM CHASER (NCT04625972). The PROVENT[1] study is a Phase III randomised, double-blind, placebo-controlled study investigating the safety and efficacy of EVUSHELD for pre-exposure prophylaxis of COVID-19. This study includes over 5,000 people, of which 78% had baseline co-morbidities or characteristics associated with an increased risk for severe COVID 19. EVUSHELD reduced the incidence of positive symptomatic illness (COVID-19) when compared to placebo by 77% (at 3 months analysis) and 83% (at 6 months analysis).

In PROVENT 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. None of the cardiac disorder SAEs in the EVUSHELD group were considered related to the investigational medicinal product by the Investigator.

STORM CHASER study is a Phase III randomised, double-blind, placebo-controlled study to determine the safety and efficacy of EVUSHELD in post-exposure prophylaxis of COVID-19. This study included over 1,000 people, at 6 months follow up. No cardiac SAEs were reported (median follow-up approximately 6 months) in STORM CHASER.

In STORM CHASER, the subjects were younger (median age 48 versus 57 years) and had less baseline risk factors for heart disease compared to PROVENT (24 % versus 36% with hypertension, 11% versus 14 % with diabetes, and 3% versus 8% with cardiovascular disease in STORM CHASER versus PROVENT, respectively).

Prior to starting EVUSHELD in patients with a high risk for cardiovascular events, healthcare providers should consider the risks and benefits. They should also recommend patients to seek immediate medical assistance if they develop any signs or symptoms that might indicate a cardiovascular event.

The safety information concerning these cardiovascular events are included in the EVUSHELD FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab), under Section 5 Warnings and Precautions:

Call for reporting

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to EVUSHELD.

Submit adverse event and medication error reports, using one of the following methods:

- Directly to AstraZeneca patient Safety:
  Email: ksa.ae@astrazeneca.com - Phone: +966 11 2249235
  Portal: https://contactazmedical.astrazeneca.com
- SFDA reporting information:
  Email: npc.drug@sfda.gov.sa -Toll free phone: 19999 - Portal: https: //ade.sfda.gov.sa

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA

Reference(S)

1) Levin MJ, Ustinaowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. N Engl J Med. 2022(suppl appendix). DOI: 10.1056/NEJMoa2116620

Best Regards,
Malak Alshammari
Saudi QPPV

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