Emergency Use Authorization (EUA) for EVUSHELD

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number(s)	000104
Date of Memorandum	April 1, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	AstraZeneca Pharmaceuticals LP Stacey Cromer Berman, PhD Senior Regulatory Affairs, Director and Team Lead One MedImmune Way Gaithersburg, MD 20878 Phone: (b) (6) Email: (b) (6)
Original Authorization	December 8, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	EVUSHELD
Established Name/Other names used during development	AZD7442 (tixagevimab, AZD8895) injection; (cilgavimab, AZD1061) injection, co-packaged for intramuscular use
Dosage Forms/Strengths	Tixagevimab 300 mg/3 mL (100 mg/mL) IM Cilgavimab 300 mg/3 mL (100 mg/mL) IM
Therapeutic Class	SARS-CoV-2 spike protein-directed attachment inhibitor
Intended Use or Need for EUA	Pre-exposure prophylaxis of COVID-19

Intended Population(s)	Adults and pediatric individuals (12 years of age and older weighing at least 40 kg):
	• Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
	  • Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
	  • For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, 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).

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Rationale for Revisions to EUA Fact Sheets

The EVUSHELD EUA fact sheet for healthcare providers is being revised at this time, and a Dear Healthcare Provider Letter communicating these changes is being issued, to provide dosing recommendations for individuals who initially received the previously authorized dose (150 mg of tixagevimab and 150 mg of cilgavimab) and were unable to receive a second dose as recommended within 3 months.

As background, EVUSHELD initially received an emergency use authorization (EUA) on December 8, 2021, for the pre-exposure prophylaxis (PrEP) of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and who either may not mount an adequate immune response to COVID-19 vaccination due to moderate to severe immune compromise or for whom vaccination against COVID-19 is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components. This previously authorized EVUSHELD dose was 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab) administered as consecutive intramuscular injections.

On February 24, 2022, the authorized EVUSHELD dose was modified to 600 mg EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) based on neutralization assays demonstrating reduced activity of EVUSHELD against the Omicron BA.1 and BA.1.1 subvariants, which made up the majority of circulating SARS-CoV-2 in the United States by the beginning of 2022. As part of that revision, the Fact Sheet for Healthcare Providers stated that individuals who have already received the previously

authorized dose (150 mg of tixagevimab and 150 mg of cilgavimab) should receive a second EVUSHELD dose (150 mg of tixagevimab and 150 mg of cilgavimab) as soon as possible. As EVUSHELD had only been available to individuals for a short period, it was thought that everyone would be able to receive this second dose within a few months of their first dose.

This current update is to provide recommendations for individuals who were not able to receive this second dose within three months of their first dose. Based on comparative PK modeling analyses (described below), individuals unable to receive this second dose by 3 months after the initial dose should instead be dosed with 300 mg of tixagevimab and 300 mg of cilgavimab.

Population PK model-based simulations were conducted to obtain predicted maximum serum AZD7442 concentrations in the adult population. Comparisons were made of the predicted geometric mean serum AZD7442 C_{max} values following various re-dosing scenarios of EVUSHELD (i.e., Dose 2) to the predicted geometric mean serum AZD7442 C_{max} values following an initial dose of EVUSHELD of 300 mg of tixagevimab and 300 mg of cilgavimab (i.e., Dose 1) (C_{max} ratio = Dose 2 C_{max} / Dose 1 600 mg C_{max}). For decision making, a default no-effect boundary of 80% to 125% was used for the serum AZD7442 C_{max} ratio - an interval within which a change in the systemic exposure measure is considered not significant enough to warrant clinical action. This approach ensures similar exposures among all individuals with various dosing intervals. At this time, there are no specific safety concerns associated with higher Cmax values.

Comparative PK modeling evaluations are reported in **Table 1**. The serum AZD7442 C_{max} ratio fell below 80% suggesting possible efficacy concerns in individuals who had previously received the authorized EVUSHELD dose of 150 mg of tixagevimab and 150 mg of cilgavimab and then received a subsequent EVUSHELD dose of 150 mg of tixagevimab and 150 mg of cilgavimab around 3 months. Alternatively, if the previously authorized dose of 150 mg of tixagevimab and 150 mg of cilgavimab is followed 3 months later by a subsequent dose of 300 mg of tixagevimab and 300 mg of cilgavimab, the serum AZD7442 C_{max} ratio was approximately 125% suggesting acceptable drug concentration-driven safety risks in these individuals.

Table 1: Comparisons of AZD7442 C_{max} Ratios (Dose 2 C_{max} / Dose 1 600 mg C_{max}) After Various Re-Dosing Scenarios of EVUSHELD Intramuscular Administration Following Authorization of the Adjusted Dosing Regimen

EVUSHELD* Dosing Regimen	**Dose 2 C_{max} / Dose 1 600 mg C_{max}** GeoMean Ratio (%) (90% CI)
300 mg then 300 mg 1 month later	91 (90.2 – 91.9)
300 mg then 300 mg 2 months later	82.8 (82.1 – 83.6)
300 mg then 300 mg 3 months later	76.3 (75.6 – 77.0)
300 mg then 300 mg 4 months later	71.0 (70.4 – 71.7)
300 mg then 300 mg 5 months later	66.9 (66.3 – 67.5)
300 mg then 300 mg 6 months later	63.6 (63.0 – 64.2)

300 mg then 600 mg 1 month later	140.0 (138.7 – 141.3)
300 mg then 600 mg 2 months later	131.9 (130.7 – 133.1)
300 mg then 600 mg 3 months later	125.6 (124.4 – 126.7)
300 mg then 600 mg 4 months later	120.4 (119.3 – 121.5)
300 mg then 600 mg 5 months later	116.3 (115.3 – 117.4)
300 mg then 600 mg 6 months later	113.1 (112.0 – 114.1)

*EVUSHELD 300 mg dose (150 mg of tixagevimab and 150 mg of cilgavimab); EVUSHELD 600 mg dose (300 mg of tixagevimab and 300 mg of cilgavimab)
Cmax = maximum serum concentration of drug; GeoMean = geometric mean; CI = confidence interval

AZD7442 concentration = the sum of the tixagevimab and cilgavimab concentrations

Comparisons were made with an analysis of variance (ANOVA) model using logarithms (Log_{10}) of the data. The point estimates and confidence limits were exponentiated back to the original scale.

Summary of Fact Sheet Revisions:

Section 2.1 of the Fact Sheet for Healthcare Providers was updated to specify the following dosing for individuals who initially received 150 mg of tixagevimab and 150 mg of cilgavimab:

Individuals who have already received the previously authorized initial dose (150 mg of tixagevimab and 150 mg of cilgavimab) ***should receive an additional EVUSHELD dose as soon as possible, with the dose based on the following criteria:***

- *If the patient received their initial dose ≤ 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab, refer to Table 2 below.*
- *If the patient received their initial dose > 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab, refer to Table 1 below.*

In addition, edits were made to Sections 2.3 and 17 of the Fact Sheet for Healthcare Providers to be consistent with these changes.

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommends revisions to EUA 104 as outlined above in order to best protect public health and to provide health care providers with the most current recommendations about EVUSHELD.

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/s/

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