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	January 26, 2023
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 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 and Other Documents

The EVUSHELD EUA Fact Sheet for Healthcare Providers; Fact Sheet for Patients, Parents and Caregivers; and Letter of Authorization are being revised at this time for the following reasons:

1. **To update the EVUSHELD neutralization activity data against SARS-CoV-2 viral variants in Section 12.4 of the EUA Fact Sheet for Healthcare Providers**
   This update to Section 12.4 (Microbiology) provides the results of cell culture neutralization activity assays of EVUSHELD against the SARS-CoV-2 Omicron subvariant XBB.1.5, which is currently the most prevalent subvariant circulating in the United States (U.S.) with a frequency of 49.1%. EVUSHELD is not anticipated to be active against XBB.1.5.

2. **To add a limitation of authorized use (LOAU) related to the national frequency of SARS-CoV-2 variants that are not susceptible to EVUSHELD.**
   Based on the national prevalence of non-susceptible variants, and consistent with the LOAU as further described below, FDA has determined that EVUSHELD is not authorized in the U.S. until further notice by the Agency.

   Background on Regulatory History
   On December 8, 2021, EVUSHELD (tixagevimab co-packaged with cilgavimab) received an emergency use authorization (EUA) for the pre-exposure prophylaxis

(PrEP) of coronavirus disease 2019 (COVID-19) in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination or for whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components. At that time, the authorized dose for EVUSHELD was 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab) administered as consecutive intramuscular (IM) injections, which was the dose evaluated in the Phase 3 trial PROVENT in which EVUSHELD used as PrEP demonstrated a relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness of 77% compared to placebo. During the primary analysis period of PROVENT when these efficacy analyses took place, predominant SARS-CoV-2 variants were Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Epsilon (B.1.429).

At the time of the original authorization, the SARS-CoV-2 Omicron variant (subvariant B.1.1.529 [BA.1]) had just emerged and neutralization activity of EVUSHELD against Omicron subvariant BA.1 was unknown. In the subsequent weeks, cell culture neutralization assays demonstrated reduced activity of EVUSHELD against Omicron subvariants BA.1 and BA.1.1 (BA.1+R346K) compared to the wild-type reference strain. In addition, by the end of December 2021, the Omicron BA.1 subvariant was increasing in prevalence in the U.S. Consequently, in a revised authorization on February 24, 2022, using pharmacokinetic (PK) and pharmacodynamic (PD) modeling assessments to predict an adequate dose for PrEP and supported by existing safety data of the 600 mg EVUSHELD dose from the Phase 3 COVID-19 treatment trial TACKLE, the originally authorized EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) was increased to 600 mg EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) for PrEP to increase the likelihood of attainment of a minimum protective concentration based on cell culture neutralization activity of EVUSHELD against the circulating Omicron subvariants.[1]

Subsequently on June 29, 2022, 6-month repeat dosing recommendations of the 600 mg EVUSHELD dose were added to the authorized Fact Sheets. This revision was based on PK/PD modeling using the EVUSHELD neutralization data against the Omicron subvariants BA.4 and BA.5. The subvariants BA.4 and BA.5 made up 13% and 43%, respectively, of the circulating variants in the U.S. at that time and were increasing in proportion. In addition, EVUSHELD neutralization activity was lower against BA.4 and BA.5 than against BA.2 and BA.2.12.1, the other prevalent Omicron subvariants circulating in the U.S. at that time. The

[1] See CDER's February 24, 2022 summary review supporting the revision to EUA 104 at: https://www.fda.gov/media/156674/download.

PK/PD model used the lower neutralization against BA.4 and BA.5 in order to provide a more conservative estimate for adequate dosing to ensure coverage against the other circulating Omicron subvariants.

At the time of the June 29, 2022, EUA revision, EVUSHELD was expected to have neutralization activity against all known circulating variants. However, since that time, the epidemiological landscape has shifted with the emergence of multiple Omicron subvariants that are co-circulating in the U.S. Specifically, cell culture neutralization activity assessments of EVUSHELD against several recently emergent Omicron subvariants show a >1,000-fold reduction in activity for both component monoclonal antibodies (cilgavimab and tixagevimab), indicating that EVUSHELD is unlikely to be active against these subvariants.

Consequently, on October 3, 2022, the EUA was revised to add a warning about the increased risk for developing COVID-19 if an individual receiving EVUSHELD was exposed to variants of SARS-CoV-2 that are not neutralized by EVUSHELD. At the time, FDA also revised the authorized Fact Sheets to add neutralization activity data for BA.2.75, BA.4.6, and BA.5. Subsequently, on November 17, 2022, the EUA was revised to add EVUSHELD neutralization activity data against BA.2.75.2, BF.7, BJ.1, BQ.1, and BQ.1.1. On December 21, 2022, the EUA was revised again to add EVUSHELD neutralization activity data against BA.5.2.6, BN.1, BF.11, and XBB.

Rationale for the Revisions

Consistent with section 564(g) of the Federal Food, Drug & Cosmetic Act, the Agency will periodically review the appropriateness and circumstances of each EUA.[2] As part of its ongoing assessment of the circumstances and appropriateness of the EUA for EVUSHELD, FDA has continued to monitor for the emergence of viral variants of SARS-CoV-2 and their potential impact on the neutralization activity of EVUSHELD.

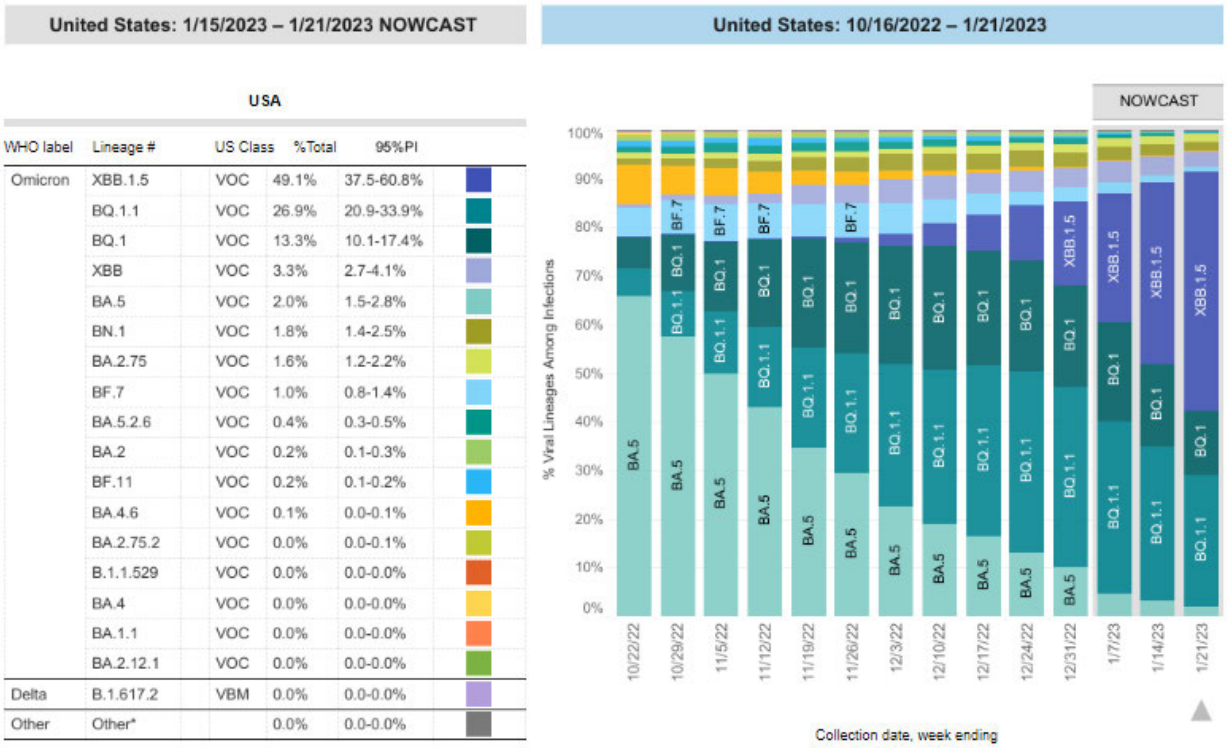
At the time of this review, the most recent surveillance data based on the CDC's Nowcast Model[3] indicate that Omicron subvariants that are non-susceptible to EVUSHELD are estimated to account for 94.3% of the SARS-CoV-2 sequences nationally for the week ending January 21, 2023.[4] This calculation includes the following SARS-CoV-2 Omicron subvariants against which EVUSHELD is unlikely to be active (please see Section 12.4 of the Fact Sheet for Healthcare Providers for more details): XBB.1.5, BQ.1.1, BQ.1, XBB, BF.7, BA.5.2.6, BF.11,

[2] See section 564(g)(1) of the Federal Food, Drug & Cosmetic Act.

[3] The CDC Nowcast Model uses available data to estimate the proportions of circulating variants in the United States. This information facilitates timely public health action. Currently, Nowcast is our best tool to predict the prevalence of circulating SARS-CoV-2 variants in real time.

[4] See Figure 1.

BA.4.6, and BA.2.75.2. The Nowcast data has demonstrated a sustained increase of the proportion of non-susceptible variants over the last several weeks.



WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	49.1%	37.5-60.8%
	BQ.1.1	VOC	26.9%	20.9-33.9%
	BQ.1	VOC	13.3%	10.1-17.4%
	XBB	VOC	3.3%	2.7-4.1%
	BA.5	VOC	2.0%	1.5-2.8%
	BN.1	VOC	1.8%	1.4-2.5%
	BA.2.75	VOC	1.6%	1.2-2.2%
	BF.7	VOC	1.0%	0.8-1.4%
	BA.5.2.6	VOC	0.4%	0.3-0.5%
	BA.2	VOC	0.2%	0.1-0.3%
	BF.11	VOC	0.2%	0.1-0.2%
	BA.4.6	VOC	0.1%	0.0-0.1%
	BA.2.75.2	VOC	0.0%	0.0-0.1%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2, BN.1,XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except XBB.1.5, sublineages of XBB are aggregated to XBB. For all the lineages listed in the above table, their sublineages are aggregated to the listed parental lineages respectively. Previously, XBB.1.5 was aggregated to XBB. Lineages BA.2.75.2, XBB, XBB.1.5, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

Figure 1: CDC Nowcast data ending the Week of January 21, 2023, source: https://covid.cdc.gov/covid-data-tracker/#variant-proportions (accessed January 23, 2023)

To date, EVUSHELD has been the only product authorized or approved for the pre-exposure prophylaxis (PrEP) of COVID-19 for individuals who either are unlikely to benefit from COVID-19 vaccination due to moderate to severe immune compromise or who are unable to receive COVID-19 vaccinations due to a history of adverse reaction to the COVID-19 vaccine or one of its components.

Under its authorization, EVUSHELD must be administered to an eligible individual prior to exposure to SARS-CoV-2 and is expected to provide protection against infection by susceptible variants of SARS-CoV-2 over a 6-month time period after the date of administration. During this time, individuals may be exposed to multiple new and evolving SARS-CoV-2 variants with varying susceptibility profiles to the product. The Agency recognizes that the epidemiological landscape of circulating variants has greatly shifted over time

and recently has resulted in the overwhelming majority of circulating variants no longer being susceptible to EVUSHELD. Given this, and taking into consideration the known risks of EVUSHELD (e.g., hypersensitivity reactions including anaphylaxis), the benefit-risk assessment for the continued authorization of EVUSHELD for PrEP is no longer favorable at this time. The Agency further recognizes that the epidemiological landscape may shift in the future such that known susceptible variants may increase in prevalence, or new susceptible variants may emerge, to a threshold where the benefit-risk assessment of EVUSHELD for PrEP is favorable once again. In considering the above, FDA believes that the inclusion of a Limitation on the Authorized Use (LOAU) of EVUSHELD reflecting the balance of these benefit risk considerations is appropriate to protect the public health.

As such, the Division of Antivirals and Office of Infectious Diseases recommends adding the following new LOAU for EVUSHELD:

> EVUSHELD is authorized for use only when the combined frequency of non-susceptible variants nationally is less than or equal to 90%, based on available information including variant susceptibility to EVUSHELD and national variant frequencies.

In implementing this LOAU, FDA will monitor conditions to determine whether use nationally is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (e.g., section 12.4 of authorized Fact Sheet for Health Care Providers), and CDC national variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination(s) and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. The Limitations of Authorized Use proposed above will ensure that, based on available information including variant susceptibility to EVUSHELD, the benefit-risk assessment remains favorable for any individual receiving this drug when use is consistent with the terms and conditions of the authorization.

Consistent with the above, and based on the most recent Nowcast data showing greater than 90% circulation of variants that are non-susceptible to EVUSHELD[5], FDA has determined that EVUSHELD is not currently authorized for use in the United States until further notice by the Agency.

FDA has issued EUAs authorizing certain antiviral monoclonal antibody therapies for the treatment and/or post-exposure prophylaxis (PEP) of COVID-19 containing an LOAU that limited their use to only when a patient in the authorized population is likely to have been infected with, or exposed to, as applicable to the

[5] See Figure 1.

authorized use, a variant that is susceptible to the authorized treatments. We note that the LOAU being proposed for EVUSHELD is different from the LOAU that FDA has included as part of the authorization of mAbs for treatment or PEP; however, such differences are necessary due to the distinct benefit-risk considerations associated with their respective uses. It is important to note that there are no alternative prevention options for the population for whom EVUSHELD is authorized (i.e., for individuals who either are unlikely to benefit from COVID-19 vaccination due to moderate to severe immune compromise or who are unable to receive COVID-19 vaccinations due to a history of adverse reaction to the COVID-19 vaccine or one of its components). For the EVUSHELD authorized population, we have determined that benefit-risk is no longer favorable for use when the combined frequency of non-susceptible variants nationally is greater than 90%, based on available information including variant susceptibility to EVUSHELD and national variant frequencies. In our assessment, at that time, the risk of exposing patients to possible side effects of EVUSHELD such as hypersensitivity reactions (including anaphylaxis), which can be potentially serious, is no longer balanced by the anticipated benefit of the product in reducing the risk of symptomatic infection.

Unlike PrEP, administration of a mAb for treatment or PEP occurs only after acute infection or a known recent exposure, respectively, and the authorized uses involve prompt administration of the mAb. Notably, and most relevant to treatment uses, there are no authorized or approved point-of-care tests that can expeditiously determine the SARS-CoV-2 variant that a patient is infected with in order to guide time-sensitive treatment decisions. As such, epidemiological data available at the time provides the greatest certainty as to the expected benefit for a particular therapy when used for treatment or PEP at the time therapy is considered. We also note that there are currently several therapies authorized or approved for the treatment of mild-to-moderate COVID-19 in certain high-risk patients, including Paxlovid, Veklury, and Lagevrio, whereas there are no alternative prevention options for the population within the scope of the EUA for EVUSHELD.

3. **To revise one of the Conditions of Authorization (COA) in the Letter of Authorization**

With the original EUA, the following COA was included: *Monthly aggregate reports for serious adverse events in the Cardiac Disorder System Order Class (SOC) and other non-cardiac thrombotic serious adverse events*. Based on this COA, the Sponsor has submitted monthly safety reports for the past 12 months, none of which have led to any changes in the warning in the authorized labeling regarding the imbalance of cardiovascular events observed in the pivotal clinical trial. At this time, over 2 million units of EVUSHELD have been distributed globally, the monthly cases of cardiac and thromboembolic serious adverse

events peaked in June 2022 and have declined since that time, and, as of this action, EVUSHELD may not be administered for PrEP until further notice by the Agency. Consequently, we agree with the Sponsor's request to decrease the frequency of the safety updates to align with the every-6-month Periodic Benefit-Risk Evaluation Report. Of note, the Sponsor will still be expected to report any individual events that meet the definition of a serious adverse event to the FDA Adverse Event Reporting System (FAERS), consistent with the terms and conditions of the authorization.

Summary of Revisions:

The EVUSHELD EUA Fact Sheet for Healthcare Providers; Fact Sheet for Patients, Parents and Caregivers; and Letter of Authorization are being revised at this time to add the following LOAU:

- *EVUSHELD is authorized for use only when the combined frequency of non-susceptible variants nationally is less than or equal to 90%, based on available information including variant susceptibility to EVUSHELD and national variant frequencies[6].*

Section 12.4 (Microbiology) of the Fact Sheet for Healthcare Providers was updated to add neutralization data of cilgavimab, tixagevimab, and tixagevimab and cilgavimab in combination against virus-like particles pseudotyped with the spike glycoproteins of XBB.1.5.

The LOA was also revised to modify condition O related to serious adverse events in the Cardiac Disorder System Order Class (SOC) and other non-cardiac thrombotic serious adverse events to read as follows:

- *Biannual (every 6 months) aggregate reports for serious adverse events in the Cardiac Disorder System Order Class (SOC) and other non-cardiac thrombotic serious adverse events*

Regulatory Conclusion and Associated Actions:

The Division of Antivirals and Office of Infectious Diseases recommend revisions to EUA 104 as outlined above in order to best protect public health. Consistent with the new LOAU, EVUSHELD is not currently authorized for emergency use in the U.S. at this time. FDA will communicate publicly on the FDA website that EVUSHELD is not authorized for use in the U.S. and, therefore, may not be administered for PrEP of COVID-19 under the EUA until further notice by the Agency.

[6] FDA will monitor conditions to determine whether use is consistent with the scope of authorization, referring to available information, including information on variant susceptibility (e.g., Section 12.4 of the authorized Fact Sheet for Healthcare Providers) and CDC variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

The Agency will continue monitoring circulating variants that may impact the use of EVUSHELD and provide updates as new information becomes available.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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