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	October 3, 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 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 and Fact Sheet for Patients, Parents, and Caregivers are being revised at this time for the following reasons:

1. **To update the Fact Sheet for Healthcare Providers and the Patient Fact Sheet with the risk of COVID-19 due to SARS-CoV-2 Viral Variants with Reduced Susceptibility to EVUSHELD**

   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, in vitro neutralization assays demonstrated reduced activity of EVUSHELD against Omicron subvariants BA.1 and BA.1.1 (BA.1+R346K) compared to wild type reference strain. In addition, by the end of December 2021, the Omicron BA.1 subvariant was increasing in prevalence in the United States (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 in vitro neutralization activity of EVUSHELD against the circulating Omicron subvariants.

Subsequently on June 29, 2022, 6-month repeat dosing recommendations of the 600 mg EVUSHELD dose were added 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 United States 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 in the United States at that time, so using neutralization activity against BA.4 and BA.5 in the PK/PD modeling provided a more conservative estimate for adequate dosing.

Rationale for the Revision

At that time of the June 29, 2022, EUA revision, there were no known circulating variants against which EVUSHELD did not have neutralization activity. However, recent in vitro neutralization activity of EVUSHELD against the Omicron subvariant BA.4.6 shows a >1,000-fold reduction in activity for both component monoclonal antibodies (cilgavimab and tixagevimab), indicating that EVUSHELD is unlikely to be active against this subvariant. The BA.4.6 subvariant first emerged in the U.S. in late June 2022, has been increasing in prevalence, and made up 12% of circulating variants in the U.S. as of September 24, 2022[1]. The

[1] Prevalence numbers are from the Nowcast estimates from the CDC COVID Data Tracker website accessed on 9/29/22 (link: https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

BA.5 subvariant, against which EVUSHELD retains neutralization activity, still made up 83% of circulating variants in the U.S. as of September 24, 2022. BF.7, another emerging subvariant present at a frequency of about 2% in the U.S. as of September 24, 2022, has the same receptor binding domain amino acid sequence as BA.4.6 and is likely also resistant to neutralization by EVUSHELD, although the neutralization activity of EVUSHELD against this subvariant has not yet been evaluated. In addition, preliminary data for other Omicron subvariants with key substitutions within the receptor binding domain, most notably substitutions at R346 or K444 and F486, indicate that there may be multiple emerging subvariants that may not be neutralized by EVUSHELD, such as BA.2.75.2, BA.4.7, BA.5.2.7, BA.5.6.2, and BA.5.9[2,3,4], although these variants are infrequently reported (<1%) in the U.S. as of September 24, 2022. The authorized EVUSHELD Fact Sheets will be updated as more data become available.

EVUSHELD is currently the only authorized or approved product in the U.S. for PrEP of COVID-19 in individuals 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. As a prophylactic product with an extended half-life of around 85 days, EVUSHELD is intended to protect against both current and future variants. It is unknown at this time whether the Omicron BA.4.6 subvariant will outcompete the currently dominant EVUSHELD-susceptible subvariants, or whether EVUSHELD will retain neutralization activity against novel variants that become dominant in the future.

Because EVUSHELD is not expected to provide protection against all currently circulating Omicron subvariants, a warning and precaution about the increased risk for COVID-19 due to exposure to SARS-CoV-2 viral variants not neutralized by EVUSHELD, compared to variants that are neutralized by EVUSHELD, is being added to the Factsheet for Healthcare Providers with instructions to advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate, if signs or symptoms of COVID-19 occur. This risk was also added to the Factsheet for Patients, Parents, and Caregivers, and a Dear Healthcare Provider Letter is also being distributed to alert healthcare

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[2] Cao Y et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. bioRxiv 2022.09.15.507787; doi: https://doi.org/10.1101/2022.09.15.507787

[3] Jian et al. Further humoral immunity evasion of emerging SARS-CoV-2 BA.4 and BA.5 subvariants. bioRxiv 2022.08.09.503384; doi: https://doi.org/10.1101/2022.08.09.503384

[4] Sheward et al. Omicron sublineage BA.2.75.2 exhibits extensive escape from neutralising antibodies. bioRxiv 2022.09.16.508299; doi: https://doi.org/10.1101/2022.09.16.508299

providers of this risk. In addition, Section 12.4 (Microbiology) of the Factsheet for Healthcare Providers is being updated with new neutralization data against recent Omicron subvariants (BA.2.7.5, BA.4.6, and BA.5).

2. **To update the Fact Sheet for Healthcare Providers with an expanded list of examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination**

Immune compromise is a very broad and heterogeneous category, and not all immunocompromising conditions may lead to an inadequate immune response to COVID-19 vaccination. Consequently, at the time of the initial authorization, in order to provide guidance to healthcare providers on which individuals have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination, we used the CDC's list of moderate and severe immunocompromising conditions and treatments for which an additional primary dose of COVID-19 vaccination is recommended to guide the use of EVUSHELD under its EUA[5]. Both on the CDC website and in the EUA Factsheet for Healthcare Providers, a caveat was included that the medical conditions or treatments that may result in moderate to severe immune compromise included these listed conditions but were not limited to these listed conditions. The following language was included in Section 1 (EMERGENCY USE AUTHORIZATION) of the Fact Sheet for Healthcare Providers, with the CDC website referenced for additional information:

> *Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include but are not limited to:*
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> - *Active treatment for solid tumor and hematologic malignancies*
> - *Receipt of solid-organ transplant and taking immunosuppressive therapy*
> - *Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)*
> - *Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)*
> - *Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)*

[5] See https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

- *Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)*

It was recently brought to our attention by the Transplant Recipients and Immunocompromised Patient Advocacy Group (TRAIPAG) that some medical centers and physicians are interpreting the list as exclusive and denying EVUSHELD to other patients with moderate to severe immune compromise who may benefit. TRAIPAG noted that the COVID-19 treatment guidelines issued by NIH include several other examples on their list of people who are moderately or severely immunocompromised[6], and they asked if the NIH COVID-19 treatment guidelines examples could be included in the EVUSHELD Factsheet for Healthcare Providers. In addition to the medical conditions or treatments that may result in moderate to severe immune compromise that are already listed on the EVUSHELD Factsheet for Healthcare Providers, the NIH COVID-19 treatment guidelines include the following examples:

- Hematologic malignancies that are associated with poor responses to COVID-19 vaccines or an increased risk of severe COVID-19 regardless of the treatment status for the hematologic malignancy.
- Receipt of an islet cell transplant and are receiving immunosuppressive therapy.
- Expanded listing of examples of moderate or severe primary immunodeficiency to include common variable immunodeficiency disease (CVID) and severe combined immunodeficiency (SCID).

We met with members of the NIH COVID-19 treatment guidelines panel involved in drafting the section of the guidelines specific to immunocompromised populations. The following rationales were discussed for including the additional examples:

- Islet cell transplant recipients are often on the same immunosuppressive medications as solid organ transplant recipients, yet islet cell transplant recipients are sometimes not included under the umbrella of solid organ transplant recipients.
- Individuals with CVID and SCID regularly require immunoglobulin infusions and so would be one of the populations likely to not mount an adequate immune response to COVID-19 vaccination. Consequently, it is

[6] See https://www.covid19treatmentguidelines.nih.gov/special-populations/immunocompromised/.

appropriate to specifically include CVID and SCID as examples of severe primary immunodeficiencies.

- Patients with hematologic malignancies have had poor antibody responses to the COVID-19 vaccines in general and are a population at particularly high risk for progression to severe COVID-19, including hospitalization or death. Although published studies in patients with hematologic malignancies indicate that the antibody response to COVID-19 vaccines is lower in those patients who are on active treatment for the hematologic malignancy versus those who are not on active treatment for the hematologic malignancy, the antibody response to COVID-19 vaccines is lower among patients with hematologic malignancies who are not on active treatment for the hematologic malignancy versus the general population[7,8].
- Defining the specific conditions and treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination is complex and challenging. Many individuals are on multiple immunosuppressive medications and/or have more than one immunocompromising condition. In addition, the risk for severe COVID-19 outcomes if a breakthrough infection occurs can vary widely based on other demographic factors and comorbidities.

Based on these discussions, and in order to best protect and promote public health, we are expanding the list of examples in the Fact Sheet for Healthcare Providers of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination. In addition, we are bolding the caveat about the list of examples not being all-inclusive.

Summary of Fact Sheet Revisions:

Section 1 (EMERGENCY USE AUTHORIZATION) of the Fact Sheet for Healthcare Providers was updated to add additional examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination along with associated editorial changes. The text now reads as follows:

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[7] Herzog Tzarfati K, Gutwein O, Apel A, Rahimi-Levene N, Sadovnik M, Harel L, Benveniste-Levkovitz P, Bar Chaim A, Koren-Michowitz M. BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. Am J Hematol. 2021 Oct 1;96(10):1195-1203.

[8] Terpos E, Fotiou D, Karalis V, Ntanasis-Stathopoulos I, Sklirou AD, Gavriatopoulou M, Malandrakis P, Iconomidou VA, Kastritis E, Trougakos IP, Dimopoulos MA. SARS-CoV-2 humoral responses following booster BNT162b2 vaccination in patients with B-cell malignancies. Am J Hematol. 2022 Oct;97(10):1300-1308.

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination ***include but are not limited to****:*

- *Active treatment for solid tumor and hematologic malignancies*
- *Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)*
- *Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy*
- *Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)*
- *Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)*
- *Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)*
- *Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)*

Section 5 (WARNINGS AND PRECAUTIONS) of the Fact Sheet for Healthcare Providers was updated to add the additional warning of risk for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD and to reorder the listed warnings and precautions. The new warning, being added as 5.3, is shown below:

5.3 Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD

Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. The in-vitro neutralization activity of EVUSHELD against SARS-CoV-2 viral variants is shown in Table 6 [see Microbiology (12.4)].

Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate.

Symptoms of COVID-19 may include: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea[9].

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 BA.2.7.5, BA.4, or BA.4.6., add neutralization data against authentic BA.5 virus, and add results from a recent resistance selection in cell culture study.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) was updated to add a new NDC number (this addition was reviewed separately by the Office of Biotechnology Products in the Office of Pharmaceutical Quality and found to be acceptable).

Section 17 (PATIENT COUNSELING INFORMATION) of the Fact Sheet for Healthcare Providers was updated to add information on the risk for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD.

In addition, edits were made to the patient Fact Sheet to be consistent with these changes. A Dear Health Care Provider Letter communicating the risk of breakthrough infection due to antiviral resistance is also being issued.

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 and to provide health care providers with the most current recommendations about EVUSHELD.

[9] For additional information on the symptoms of COVID-19, please see https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.

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/s/

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