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	May 17, 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 letter of authorization, Fact Sheet for Healthcare Providers, and Patient Fact Sheet are being revised at this time, and a Dear Healthcare Provider Letter communicating these changes is being issued, to provide more instruction on EVUSHELD use in individuals who have had a severe adverse reaction to one of the COVID-19 vaccines and to provide more information on the symptoms and signs seen with EVUSHELD hypersensitivity reactions.

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. At the time of authorization, the information pertaining to approved and authorized vaccines (highly efficacious, provide broader and longer-lasting immunity than monoclonal antibody injections, safety profiles more fully characterized than EVUSHELD, widely available) informed the authorized patient population for the EVUSHELD EUA such that the populations at risk of inadequate protection from COVID-19 vaccination or who could not receive COVID-19 vaccination due to severe adverse reactions were believed

to be the populations where the known and potential benefits of emergency use of EVUSHELD for PrEP outweighed the known and potential risks.

Related to the risk for hypersensitivity reactions, the fact sheets contained a contraindication for use in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of EVUSHELD. Due to one case identified as anaphylaxis by the investigator in the PrEP trial PROVENT, the Fact Sheet for Healthcare Providers specified one hour of clinical monitoring and observation after injection, and the Fact Sheet also included a warning and precaution about serious hypersensitivity reactions, including anaphylaxis, with IgG1 monoclonal antibodies like EVUSHELD.

Assessments to Support Current EVUSHELD EUA Fact Sheet Revisions

Risk of Cross-Hypersensitivity with COVID-19 Vaccines

One of the excipients in EVUSHELD is polysorbate 80 (2.4 mg of polysorbate 80 is contained in the currently authorized initial EVUSHELD dose). Polysorbate 80 is a polyethylene glycol (PEG) derivative that functions as a nonionic surfactant and emulsifier and is widely used in food, medical, and cosmetic products. The approved or authorized COVID-19 vaccines in the United States contain either polysorbate 80 (the Janssen vaccine) or PEG-2000 (the Moderna and Pfizer vaccines).

Per several recent reviews of COVID-19 vaccine allergic reactions, a suspected though not proven cause of severe allergic reaction is an IgE-mediated reaction to PEG and its derivatives, including polysorbate 80 (*Nilsson L et al. Vaccine allergy: evidence to consider for COVID-19 vaccines. Curr Opin Allergy Clin Immunol 2021; 21: 401-409*; *Laisuan W. COVID-19 Vaccine Anaphylaxis: Current Evidence and Future Approaches. Front. Allergy 2021 Dec 23;2:801322. doi: 10.3389/falgy.2021.801322.*)

In addition, the CDC's Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#appendix-e) contain the below bulleted statements on this topic. Based on the criteria used in the CDC's clinical considerations document, administration of EVUSHELD to individuals with a history of severe allergy to a COVID-19 vaccine, but who do not have a confirmed allergy to PEG or polysorbate 80, would fall under the precaution category.

- *"Polyethylene glycol (PEG) is an ingredient in both mRNA COVID-19 vaccines, and polysorbate 80 is an ingredient in Janssen COVID-19 Vaccine. PEG and polysorbate are structurally related, and cross-reactive hypersensitivity between these compounds may occur. People with a contraindication to mRNA COVID-19 vaccines (including due to a known allergy to PEG) have a precaution to Janssen COVID-19 Vaccine. Among people who received a first mRNA COVID-19 dose but for whom the second dose is contraindicated, consideration may be given to*

vaccination with Janssen COVID-19 Vaccine (administered at least 28 days after the mRNA COVID-19 dose). People with a contraindication to Janssen COVID-19 Vaccine (including due to a known allergy to polysorbate) have a precaution to mRNA COVID-19 vaccines. For people with these precautions, referral to an allergist-immunologist should be considered…In patients with these precautions, vaccination should only be undertaken in an appropriate setting under the supervision of a healthcare professional experienced in the management of severe allergic reactions."

- *"People with a history of an immediate allergic reaction to a non-COVID-19 vaccine or injectable therapy that contains multiple components, one or more of which is a component of a COVID-19 vaccine, but it is unknown which component elicited the allergic reaction, have a precaution to vaccination with that COVID-19 vaccine. These people may benefit from consultation with an allergist-immunologist who can perform a more detailed risk assessment for COVID-19 vaccine receipt and possibly allergy testing."*

Actions recommended by CDC for individuals with an allergy that qualifies as a precaution to COVID-19 vaccination include a risk assessment, a 30-minute observation period if vaccinated, and consideration of referral to an allergist-immunologist.

A review of the post-authorization reports through FAERS of hypersensitivity reactions for EVUSHELD revealed two serious hypersensitivity reactions (anaphylaxis), including one that was reported several days prior to this EUA revision, and three non-serious hypersensitivity reactions, that occurred in individuals who had reported a previous allergic reaction to a COVID-19 vaccine, as described below.

1. **Case Number 20768743-1**: A 52-year-old female "mast cell patient", with a history of anaphylaxis to all the COVID-19 vaccines (the Janssen vaccine and one of the RNA vaccines), hypertension, and immunocompromise, experienced anaphylaxis after receiving EVUSHELD (date and time not reported). Reported symptoms and signs were wheezing, whole body flushes, and hypertension, and she received 2 doses of epinephrine. She recovered.
2. **Case Number 20802645-1**: A 66-year-old female with a history of anaphylaxis to COVID vaccines experienced anaphylactic throat swelling and hoarseness within minutes after EVUSHELD administration. She required subcutaneous epinephrine and intramuscular diphenhydramine. No other details were provided.
3. **Case Number 20479731-1**: A 60-year-old female with well-controlled asthma, who had experienced nasal congestion and a cough and chest tightness immediately after her second COVID-19 vaccine which was treated with a prednisone taper, experienced coughing and chest tightness starting within 5 minutes of receiving EVUSHELD. There was no facial swelling or hives, and her vital signs and oxygen saturation were normal. She was treated with diphenhydramine and prednisone 40 mg daily. At the time of the report, which

was four days after EVUSHELD receipt, she did not feel much better and still noted chest tightness, becoming winded with exertion, a dry cough, and a hoarse and raspy voice.

4. **Case Number 20658531-1**: A 64-year-old female with a history of anaphylaxis with the Moderna vaccine experienced a likely hypersensitivity reaction about 30 minutes after receiving EVUSHELD with symptoms including heart racing/palpitations, throat tightness, and headache. She reports she has had similar reactions with other medications, but this reaction was not as severe. Her symptoms resolved with Benadryl and albuterol, and she did not need epinephrine or steroids. She was discharged home about 2 hours after the injection.
5. **Case Number 20375777-2**: A 42-year-old female with a history of allergy to the Janssen COVID-19 vaccine, other unspecified food and drug allergies, multiple sclerosis, bronchitis, and asthma, experienced "feeling different" after EVUSHELD receipt. Her symptoms, with dates and times not reported, included wheezing, getting more short of breath, and feeling tired. No other information was provided.

The current EVUSHELD Fact Sheet for Healthcare Providers includes a 60-minute observation period for all individuals receiving EVUSHELD; however, it does not contain information on the potential for a cross-hypersensitivity with the COVID-19 vaccines or recommendation for individuals with a history of severe allergic reaction to a COVID-19 vaccine to consider referral to an allergist-immunologist and to only administer EVUSHELD under the supervision of a healthcare professional with appropriate medical support to manage severe allergic reactions. In order to ensure patient safety, this information is being added, and other small edits are being made for consistency between the authorized use, population, contraindications, and warnings and precautions.

Post-Authorization Cases of Hypersensitivity Including Anaphylaxis

A warning and precaution about hypersensitivity including anaphylaxis is included in the Fact Sheet for Healthcare Providers. At the time of the initial EUA authorization, there was one subject in PROVENT with a reported adverse event of anaphylaxis, which was considered by the investigator to be related to the study drug. The AE involved a 74-year-old male with hypertension, hypercholesterolemia, and atrial fibrillation who minutes after receiving EVUSHELD experienced severe chest pain, shortness of breath, difficulty speaking, and a mild headache. He was treated with epinephrine and was later found to have increased troponin levels, for which he was admitted to the hospital for a cardiac workup. We agreed with the investigator that this case fit the protocol's definition of anaphylaxis and was likely related to study product based on timing, and also observed that there are multiple reports in the literature of anaphylactic shock inducing myocardial ischemia; please see the initial EVUSHELD EUA review from December 8, 2021. The relevant warning and precaution read, "Serious hypersensitivity

reactions, including anaphylaxis, have been observed with Human immunoglobulin G1 (IgG1) monoclonal antibodies like EVUSHELD," with subsequent reference to Section 6.1 where this case was described.

In the months since EVUSHELD was authorized, there have been eleven separate reports of anaphylaxis and/or events that meet anaphylaxis criteria following EVUSHELD administration irrespective of any past allergic reaction to COVID-19 vaccines (FAERS cases 20461180, 20468282, 2037125, 20711320, 20739245, 20735466, 20626705, 20606498, 20768743, and 20802645 and a report from the ToxIC Registry). In addition, there have been reports of other hypersensitivity reactions necessitating transport to the emergency department and/or hospitalization occurring minutes to several hours after EVUSHELD administration. Signs and symptoms described in these reports include the following: dyspnea, chills, fatigue, tachycardia, chest pain or discomfort, nausea/vomiting, angioedema, dizziness, urticaria, wheezing, pruritus, flushing, asthenia, hyperhidrosis, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), and throat irritation.

To better inform patients and healthcare providers that anaphylaxis has been reported specifically with EVUSHELD, the warning will be revised to read, "Serious hypersensitivity reactions, including anaphylaxis, have been observed with EVUSHELD." In addition, a listing of signs and symptoms that may be seen with EVUSHELD hypersensitivity reactions will be added for consistency with EUA fact sheets for other SARS-CoV-2 spike protein-directed attachment inhibitors.

Summary of Fact Sheet Revisions:

Section 1 (EMERGENCY USE AUTHORIZATION) of the Fact Sheet for Healthcare Providers was updated to:

- Remove "(e.g., severe allergic reaction)" from the indicated population of individuals 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(s) and/or COVID-19 vaccine component(s).
- Add a cross-reference to Section 5.2 of the Warnings and Precautions.

Section 5 (WARNINGS and PRECAUTIONS) of the Fact Sheet for Healthcare Providers was updated to:

- Revise Section 5.1 (Hypersensitivity Including Anaphylaxis) to read: *Serious hypersensitivity reactions, including anaphylaxis, have been observed with EVUSHELD [see Adverse Reactions (6.1)]. Signs and symptoms of hypersensitivity reactions may include: dyspnea, chills, fatigue/asthenia, tachycardia, chest pain or discomfort, nausea/vomiting, angioedema, dizziness, urticaria, wheezing, pruritus, flushing, hyperhidrosis, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), or throat irritation.*

Administration of EVUSHELD should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. 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 1 hour.

- Add Section 5.2 (Risk of Cross-Hypersensitivity with COVID-19 Vaccines), which reads: *EVUSHELD contains polysorbate 80, which is in some COVID-19 vaccines and is structurally similar to polyethylene glycol (PEG), an ingredient in other COVID-19 vaccines [see Description (11)]. For individuals with a history of a severe hypersensitivity reaction to a COVID-19 vaccine, consider consultation with an allergist-immunologist prior to EVUSHELD administration.*

  Administration of EVUSHELD should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. 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 1 hour.

In addition, edits were made to Sections 2.3 and 4 of the Fact Sheet for Healthcare Providers and to the patient Fact Sheet and Letter of Authorization to be consistent with these changes. A Dear Health Care Provider Letter communicating the addition of the warning and precaution about the risk of cross-hypersensitivity with COVID-19 vaccines is also being issued.

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.

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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