SEE ATTACHED ADDENDUM

Emergency Use Authorization (EUA) for
EVUSHELD

Center for Drug Evaluation and Research (CDER) Memorandum

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)[1]	EUA 000104
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)
Manufacturer	AstraZeneca Pharmaceuticals LP
Review Completion Date	February 24, 2022
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Timothy Bensman, PharmD, PhD – Clinical Pharmacology Reviewer, Division of Infectious Disease Pharmacology (DIDP), Office of Clinical Pharmacology (OCP) Su-Young Choi, PharmD, PhD – Clinical Pharmacology Team Lead, DIDP/OCP Kellie Reynolds, PharmD – Division Director, DIDP/OCP John Farley, MD, MPH, Director, Office of Infectious Diseases (OID) Adam Sherwat, MD, Deputy Director, OID Debra Birnkrant, MD, Director, DAV Yodit Belew, MD, Deputy Director (Acting), DAV Poonam Mishra, MD, Deputy Director for Safety, DAV Sarah Connelly, MD- Cross Discipline Team Lead, Division of Antivirals (DAV) Stephanie Troy, MD – Clinical Reviewer, DAV Damon Deming, PhD- Clinical Virology Reviewer, DAV Jules O'Rear, PhD – Clinical Virology Team Lead, DAV Stacey Min, PharmD, ADL, DAV

	Andrew Leboeuf, JD, MS, Associate Director for Policy (Acting) Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager, Division of Regulatory Operations for Infectious Diseases (DRO-ID) Melina Fanari, R.Ph., DMEPA Safety Evaluator Sevan Kolejian, PharmD, MBA, BCPPS, DMEPA Safety Team Lead Sharon Mills, BSN, RN, CCRP, Senior Patient Labeling Reviewer, Division of Medical Policy Programs
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 150 mg/1.5 mL (100 mg/mL) IM Cilgavimab 150 mg/1.5 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)	Pre-exposure prophylaxis 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 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).

I. Rationale and Revisions to EUA Fact Sheets

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 adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are not currently infected with SARS-CoV-2, who have not had a known recent exposure to an individual infected with SARS-CoV-2, and either: 1) who have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination, or 2) 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 the time of initial authorization, the authorized dose was EVUSHELD 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. The data from PROVENT were collected through May 5, 2021 for the primary analysis and through August 29, 2021 for a subsequent post-hoc analysis. During those time periods, 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). Although no safety or efficacy data with repeat dosing were available at the time of the authorization, the totality of the scientific evidence at that time supported that the EVUSHELD 300 mg IM (150 mg of tixagevimab and 150 mg of cilgavimab) dose may be effective for PrEP for 6 months post-administration and supported a dosing interval every 6 months.

The Omicron variant (B.1.1.529 [BA.1]) had just emerged at the time of the initial authorization for EVUSHELD, and at that time the neutralization activity of EVUSHELD against Omicron BA.1 was unknown. In the subsequent weeks, in vitro neutralization assays demonstrated reduced activity of EVUSHELD against Omicron BA.1 and BA.1.1 (BA.1+R346K) compared to wild type reference strain. In addition, by January 2022, Omicron BA.1 and BA.1.1 accounted for the majority of SARS-CoV-2 infections in the United States. Consequently, we reviewed the available data to assess whether the authorized EVUSHELD 300 mg IM (150 mg of tixagevimab and 150 mg of cilgavimab) dose and 6 month repeat dosing interval remained adequate with Omicron as the predominant variant.

EVUSHELD activity against Omicron Variants

Data from multiple laboratories indicate that Omicron BA.1 and BA.1.1 (BA.1+R346K) have reduced susceptibility to EVUSHELD relative to other SARS-CoV-2 variants. However, the magnitude of that reduction remains unclear, with the fold-changes in EC_{50} values reported for these Omicron variants relative to more susceptible variants, whether from assays using virus like particles (VLPs) pseudotyped with SARS-CoV-2 spike protein or authentic viruses, covering a greater than 10-fold range. Currently reported EC_{50} values for Omicron BA.1 and BA.1.1 range from 50.8 ng/mL to 1,488 ng/mL, and currently reported fold-reductions in susceptibility for these Omicron variants relative to more susceptible comparators range from 12-fold to 424-fold. In contrast, Omicron BA.2 retains near-full susceptibility to EVUSHELD, with reported EC_{50} values ranging from 9.8 ng/mL to 43 ng/mL, and reported fold-reductions in susceptibility relative to comparators ranging from 3- to 9-fold. A recent preprint reported that EVUSHELD does not maintain activity against VLPs pseudotyped with the spike protein of BA.2, with an EC_{50} value of

>5,000 ng/mL and a >290-fold reduction in susceptibility relative to a susceptible comparator, but these data appear to be inconsistent with data from other laboratories.

Pharmacokinetic (PK) Modeling to Predict an Adequate Dose for PrEP

Our PK modeling assessment of the available data to date predict that the currently authorized 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab) single and repeat (every 6 months) EVUSHELD IM dosing regimens are suboptimal considering the significant reduction in AZD7442 activity in cell culture against the SARS-CoV-2 Omicron subvariants BA.1 and BA.1.1 discussed above. Based on our modeling parameters, a single EVUSHELD 600 mg IM (300 mg of tixagevimab and 300 mg of cilgavimab) dose may provide 3 months duration of protection against the Omicron subvariant BA.1 and 1 to 3 months protection against BA.1.1. Therefore, the EVUSHELD IM dose will be increased to 600 mg (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 activities of EVUSHELD against the Omicron subvariants (see below). Note because of the uncertainty in forecasting future circulating subvariants in general as well as which ones will be major subvariants the repeat dosing regimen will be removed at this time and updated later when more data are available.

PK Modeling and Simulation to Support Dose Choice

Approach

Population PK model-based simulations were conducted to obtain predicted concentration-time profiles for individuals within the adult population. These predicted AZD7442 concentrations in adults were compared to target minimum protective concentration (MPC) values. MPC values were defined as AZD7442 concentrations exhibiting neutralization activities (e.g., EC_{90}) in cell-based assays.

The main objective of our analysis was to compare the percentage of people in which the target MPC is met (probability of target attainment, PTA) between the two doses, 300 mg IM (currently authorized dose, 150 mg tixagevimab and 150 mg cilgavimab) and 600 mg IM (the highest dose with an adequate safety database at this time, 300 mg tixagevimab and 300 mg cilgavimab). The PTA analyses assumed 12% or 6.5% monoclonal antibody penetration from serum to lower respiratory sites of drug action [i.e., interstitial compartment or epithelial lung lining fluid (ELF)] to estimate AZD7442 concentrations at lower respiratory sites of drug activity following administration of either 300 mg or 600 mg AZD7442 IM. For the target MPC, 90% SARS-CoV-2 inhibitory AZD7442 concentrations of cell-based viral neutralization assays (i.e., 90% effective concentration; EC_{90}) were incorporated in our modeling as the minimum required for a pre-exposure prophylactic effect in the indicated population. Additional analyses used the AZD7442 EC_{87} or AZD7442 EC_{80} values, put forward by the Sponsor, to function as the target MPC. Given the inherent uncertainties with this approach and clinical need in the authorized population under emergency use, at least 70% probability to achieve the target minimum protective concentration was used to support dose decisions (see the *Critical Assessment of Assumptions* Section below).

Omicron Subvariant BA.1

The results of target attainment simulations and analyses, assuming 12% lung penetration and a target minimum protective concentration (using the in vitro EC_{90}) associated with in vivo PrEP efficacy, are reported in Table 1. As shown, the currently authorized EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) may provide protection against Omicron subvariant BA.1 but for a reduced period (8-weeks duration of protection) (PTA 73% at Month 2). Increasing the EVUSHELD IM dose to 600 mg (300 mg tixagevimab and 300 mg cilgavimab) may provide a longer duration of protection (3 months) against Omicron subvariant BA.1 and better ensure target MPC attainment (PTA 96% at Month 3).

For individuals who have already received an initial EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) and are ≤ 3 months post-dose, we recommend an additional EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) as the PTA is 83% at Month 3 following the repeat EVUSHELD dose (data not shown). Individuals who received the initial EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) are not anticipated to be outside 3 months of dosing based on the timing of initial authorization and rollout.

Additional analyses were conducted given the uncertainty in the appropriate choice of either the AZD7442 lung penetration coeffiecient (e.g., 6.5% or 12%) assumption or the target minimum protective concentration (e.g., in vitro EC_{80}, EC_{87}, or EC_{90}) assumption and their influence on PTA results (Table 1). Regardless of the lung penetration coefficient or EC value chosen, the PTA was < 70% at Month 6 following an EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab). The PTA was < 70% at Month 3 for combinations with an in vitro EC_{87} or EC_{90} value and a 6.5% lung penetration coeffiecient following an EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab). Only use of the more favorable in vitro EC_{80} value with either a 6.5% or 12% lung penetration or EC_{87} value and 12% lung penetration resulted in PTA >70% at Month 6 following an EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab). Considering a 6.5% lung penetration of AZD7442, only the more favorable in vitro EC_{80} value combination resulted in a PTA > 70% at Month 2 following an EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab). A more favorable AZD7442 lung penetration of 12% and in vitro EC_{87} value results in PTA > 70% at Month 3 following an EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab). We note the EC87 might be reasonable to assume, given the Sponsor's in silico viral dynamics modeling re-analysis and is described in greater detail under the *Minimum Protective Concentration* Section below.

Taken together, the data support increasing the EVUSHELD IM dose to 600 mg (300 mg tixagevimab and 300 mg cilgavimab) with a probable duration of protection of 3 months for the Omicron variant BA.1. Under favorable assumptions the duration of protection may possibly be up to 6 months following EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab).

Omicron Subvariant BA.1.1

The results of target attainment simulations and analyses, assuming 12% lung penetration and a target minimum protective concentration (using the in vitro EC90) associated with in vivo PrEP efficacy, are reported in Table 2. Increasing the EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) to EVUSHELD IM dose

of 600 mg (300 mg tixagevimab and 300 mg cilgavimab) may possibly provide 1 month duration of protection against Omicron subvariant BA.1.1 using these assumptions.

Additional analyses were conducted given the uncertainty in the appropriate choice of either the AZD7442 lung penetration coeffiecient assumption or the target minimum protective concentration assumption and their influence on PTA results (Table 2). Following the currently authorized EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab) only a favorable combination of 12% lung penetration and an in vitro EC_{80} value results in PTA > 70% at Months 1 and 2. Regardless of the lung penetration coefficient or EC value chosen the PTA was < 70% at Month 3 following an EVUSHELD IM dose of 300 mg (150 mg tixagevimab and 150 mg cilgavimab). Use of a lung penetration coefficient of 6.5% and any of the in vitro EC values resulted in PTA < 70% at Month 3 following an EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab). However, a lung penetration coefficient of 12% and in vitro EC_{87} value resulted in PTA of 70% at Month 3 (but not Month 6) following an EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab). We note the EC_{87} value might be reasonable to assume, given the Sponsor's in silico viral dynamics modeling re-analysis and is described in greater detail under the *Minimum Protective Concentration* Section below.

Of note, a PTA analysis using the EC_{80} value from an in vitro SARS-CoV-2 Omicron subvariant BA.1.1. authentic live virus neutralization assay and 12% ELF penetration coefficient suggest 70% PTA at Month 1, 54% PTA at month 2, and 23% PTA at month 3 following an EVUSHELD dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab). The submitted authentic live virus assay EC_{50} value is 2.46-fold the EC_{50} value of the submitted pseudotyped virus-like particle neutralization assay. It is not known which neutralization assay accurately predicts an in vivo minimum protective concentration necessary for PrEP efficacy.

Taken together, the data support the proposed dose increase to an EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab) with a probable duration of protection of 1 month. Under favorable assumptions the duration of protection may possibly be up to 3 months against the Omicron subvariant BA.1.1. following EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab).

Omicron Subvariant BA.2

As previously stated (see *EVUSHELD activity against Omicron Variants* Section), The consensus of available susceptibility data indicates that Omicron BA.2 retains near-full susceptibility to EVUSHELD, with reported EC_{50} values ranging from 9.8 ng/mL to 43 ng/mL, and reported fold-reductions in susceptibility relative to comparators ranging from 3- to 9-fold. Therefore, if BA.2 becomes the major circulating variant, the EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab) may provider a longer (more than 3 months) duration of protection.

Conclusion

PTA analyses support an EVUSHELD IM dose of 600 mg (300 mg tixagevimab and 300 mg cilgavimab) for which there are adequate clinical safety data. The Sponsor agreed to conduct additional clinical studies with doses greater than 600 mg as a condition of

authorization to determine clinical safety in preparation to address possible future SARS-CoV-2 variants for which EVUSHELD may have reduced activity.

Critical Assessment of Assumptions

Lung Penetration Coefficient

To our knowledge only one clinical study has measured monoclonal antibody penetration from serum to lower respiratory sites of drug action (i.e., interstitial compartment or ELF). For the two monoclonal antibodies evaluated, the median penetration from serum into lung epithelial lining fluid in healthy humans was reported to be 12% or 23% depending on the monoclonal antibody [1]. Consistent with this finding, we used the Sponsor's proposed 12% monoclonal antibody penetration from serum to lower respiratory sites of drug action, but with significant reservations as we noted substantial variability in this very small ELF sub-study (median values ranged from 4% to 31% depending on the dose and analyte, and sparse samples were collected from 2 subjects per timepoint) [1]. Uncertainty in the choice of the lung penetration (or partition) coefficient is further compounded by other reports of 6.5% [2, 3] lung penetration using PBPK and 8% (range 2% to 62%) [4] lung penetration using ELF in nonhuman primates. In addition, while reports commonly cite monoclonal antibody concentrations in total lung tissue homogenate as being approximately 15% of serum, the interstitial fluid concentration is estimated to be approximately 2-fold to 4-fold lower than the total homogenized lung tissue [5, 6]. This decrease is consistent with the 6.5% lung penetration reported using PBPK [2, 3]. Thus, we conducted additional analyses to inform decision making with 6.5% lung penetration as it is an equally reasonable assumption choice in our opinion. Importantly, all of the above literature regarding lung penetration of monoclonal antibodies comes from antibodies other than AZD7442. A major limitation is that we do not know the specific lung penetration coefficient for AZD7442. Of note, the Sponsor originally utilized a nasal penetration ratio of 1.8% for AZD7442 based on measured nasal lining fluid concentrations (Clinical Study D8850C00001). Because greater perfusion to the lower respiratory tract is thought to explain the potentially greater tissue distribution compared to upper respiratory tract, focus was mainly on 6.5% and 12% lung penetration coefficients. We note that PTA results with 1.8% penetration from serum suggest no in vivo drug activity against Omicron subvariants BA.1 or BA.1.1 regardless of the EC value (e.g., EC80, EC90) used.

Minimum Protective Concentration

The Sponsor has been using in vitro EC_{80} values to guide the selection of EVUSHELD dose and assess potential clinical consequences of reduced susceptibility of EVUSHELD against Omicron variants in vitro. The use of EC_{80} value was based on in-silico SARS-CoV-2 viral dynamics modeling approach, which suggests 80% SARS-CoV-2 inhibition by AZD7442 is minimally required for a pre-exposure prophylactic effect. However, the model contains sub-models of host immune response (innate and adaptive) in addition to a drug response sub-model (Section 1.19, EUA Prophylaxis Request, Fig 26, sequence number 1, received 09-30-2021). As most persons for whom EVUSHELD is indicated will have moderate to severe immune compromise due to a medical condition or have received immunosuppressive medicines or treatments and may not mount an adequate immune response, we question the validity of including host immune response sub-models that imply host immune responses to viral infection are not impaired or absent.

Based on these concerns, the Sponsor reconducted analyses suggesting that a viral cell entry inhibition of at least 87% by AZD7442 is sufficient to keep the viral load suppressed in immunocompromised patients (AZD7442 prophylaxis EUA regulatory response, pg 19, sequence number 34, received 01-25-22). As other SARS-CoV-2 monoclonal antibody programs have used the EC_{90} value for clinical development decisions and considering the Sponsor's preceding viral dynamics modeling re-analysis results, the AZD7442-driven 90% SARS-CoV-2 inhibition as the minimal requirement for a PrEP effect is favored and supports using the EC_{90} value rather than EC_{80} value as the minimum protective concentration target. However, we conducted additional analyses with the EC_{80} and EC_{87} values.

Additional Considerations

No clinical PK-PD relationships or thresholds of protection have been identified to date for AZD7442 or other mAbs targeting SARS-CoV-2. The predictive accuracy of this translational PK-PD modeling approach is not established. Limitations of the above evidence include but are not limited to: (i) uncertainty in the in vivo validity of using in vitro EC_{80} or EC_{90} values from a microneutralization assay, for which results are likely dependent on specific conditions and platform, as the PD metric associated with clinical protection, (ii) uncertainty regarding the relevant respiratory tract site(s) of drug action (e.g., nasal or bronchoalveolar epithelial lining fluid, interstitial compartment), and (iii) uncertainty regarding the specific and accurate measurement of drug(s) at these principal sites of drug action.

Table 1: Predicted % of Participants That Will Have AZD7442[1] Concentrations ≥ a Minimum Protective Concentration Target Using the In Vitro EC80 [2] or EC87 [3] for AZD7442 Against SARS-CoV-2 Omicron Subvariant BA.1. Following Single Dose IM Administration of EVUSHELD Assuming 6.5% [4] or 12% [5] Drug Penetration from Serum to Lower Respiratory Sites of Drug Action

	Time (Months)	% of participants					
		EC80		EC87		EC90	
300 mg EVUSHELD IM		Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%
	1	91	99	60	93	30	82
	2	86	99	40	90	11	73
	3	71	98	13	80	2	47
	6	6	65	0	11	0	1
	9	0	9	0	0	0	0

	Time (Months)	% of participants					
		EC80		EC87		EC90	
600 mg EVUSHELD IM		Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%
	1	99	100	95	99	86	98
	2	99	100	93	99	80	98
	3	99	100	85	99	57	96
	6	73	98	16	82	3	51
	9	13	65	0	19	0	5

IM = intramuscular; EC80 = drug concentration that gives 80% of maximum effect; EC87 = drug concentration that gives 87% of maximum effect; EC90 = drug concentration that gives 90% of maximum effect; 300 mg EVUSHELD IM = 150 mg tixagevimab and 150 mg cilgavimab; 600 mg EVUSHELD IM = 300 mg tixagevimab and 300 mg cilgavimab)

[1] AZD7442 concentration = the sum of the tixagevimab and cilgavimab concentrations

[2] The AZD7442 driven 80% SARS-CoV-2 cell entry inhibition concentration (EC_{80}) is 836 ng/mL based on in vitro SARS-CoV-2 Omicron subvariant BA.1 authentic live virus neutralization assay: EUA Fact Sheet EC50 values from both pseudotyped virus-like particles and authentic live virus neutralization were pooled and the central tendency represented as the geometric mean. The geometric mean EC_{80} was then estimated from a concentration-response relationship assuming a Hill coefficient of 1.

[3] The AZD7442 driven 87% SARS-CoV-2 cell entry inhibition concentration (EC_{87}) is 1,398 ng/mL based on in vitro SARS-CoV-2 Omicron subvariant BA.1 neutralization assays as follows: EUA Fact Sheet EC50 values from both pseudotyped virus-l ke particles and authentic live virus neutralization were pooled and the central tendency represented as the geometric mean. The geometric mean EC_{87} was then estimated from a concentration-response relationship assuming a Hill coefficient of 1.

[4] A proportionality factor (6.5%: lung interstitial fluid or lung epithelial lining fluid to serum partitioning coefficient) from publicly available literature was applied to serum concentrations to predict lower respiratory tract drug concentrations [2,3].

[5] A proportionality factor (12%: lung interstitial fluid or lung epithelial lining fluid to serum partitioning coefficient) from publicly available literature was applied to serum concentrations to predict lower respiratory tract drug concentrations [1].

Table 2: Predicted % of Participants That Will Have AZD7442[1] Concentrations ≥ a Minimum Protective Concentration Using the In Vitro EC80 [2] or EC87 [3] Target for AZD7442 Against SARS-CoV-

2 Omicron Subvariant BA.1.1 Following Single Dose IM Administration of EVUSHELD Assuming 6.5% [4] or 12% [5] Drug Penetration from Serum to Lower Respiratory Sites of Drug Action

	Time (Months)	% of participants					
		EC80		EC87		EC90	
		Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%
300 mg EVUSHELD IM	1	31	83	2	41	0	14
	2	12	74	0	20	0	3
	3	2	48	0	4	0	0
	6	0	1	0	0	0	0
	9	0	0	0	0	0	0
	Time (Months)	**% of participants**					
		EC80		EC87		EC90	
		Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%
600 mg EVUSHELD IM	1	87	98	49	90	20	77
	2	80	98	28	86	6	63
	3	58	96	7	70	1	33
	6	3	52	0	5	0	0
	9	0	5	0	0	0	0

IM = intramuscular; EC80 = drug concentration that gives 80% of maximum effect; EC87 = drug concentration that gives 87% of maximum effect; EC90 = drug concentration that gives 90% of maximum effect; 300 mg EVUSHELD IM = 150 mg tixagevimab and 150 mg cilgavimab; 600 mg EVUSHELD IM = 300 mg tixagevimab and 300 mg cilgavimab)

[1] AZD7442 concentration = the sum of the tixagevimab and cilgavimab concentrations

[2] The AZD7442 driven 80% SARS-CoV-2 cell entry inhibition concentration (EC_{80}) is 1,864 ng/mL based on in vitro SARS-CoV-2 Omicron subvariant BA.1.1 pseudotyped virus-l ke particle neutralization assay: EC50 value was obtained (EUA000104, Table 1, Sequence number 35, received 01-26-22; corresponds 424-fold EC50 shift reported in EUA Fact Sheet). The EC_{80} was then estimated from a concentration-response relationship assuming a Hill coefficient of 1.

[3] The AZD7442 driven 87% SARS-CoV-2 cell entry inhibition concentration (EC_{87}) is 3,118 ng/mL based on in vitro SARS-CoV-2 Omicron subvariant BA.1.1 pseudotyped virus-l ke particle neutralization assay: EUA Fact Sheet EC50 values was obtained. The EC_{87} was then estimated from a concentration-response relationship assuming a Hill coefficient of 1.

[4] A proportionality factor (6.5%: lung interstitial fluid or lung epithelial lining fluid to serum partitioning coefficient) from publicly available literature was applied to serum concentrations to predict lower respiratory tract drug concentrations [2,3].

[5] A proportionality factor (12%: lung interstitial fluid or lung epithelial lining fluid to serum partitioning coefficient) from publicly available literature was applied to serum concentrations to predict lower respiratory tract drug concentrations [1].

Source: FDA Reviewer's Analysis. Applicant's NONMEM simulation model (run702801043.mod) and simulation dataset with modifications (sim_7442_600_15_months.csv) (EUA 000104, 5.3.3.5 Population PK Study Reports, SN39)

Safety Data Supporting Higher Doses

Safety Summary

The safety evaluation for the original EUA found that overall safety was similar between 300 mg IM EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) and placebo recipients. However, an imbalance was noted in the number of cardiac serious adverse events (SAEs) in the Phase 3 trial PROVENT evaluating EVUSHELD for SARS-CoV-2 PrEP, particularly events of myocardial infarction (8/3461 (0.23%) EVUSHELD recipients versus 1/1736 (0.06%) placebo recipients) and cardiac failure (6/3461 (0.17%) EVUSHELD recipients versus 1/1736 (0.06%) placebo recipients, through Day 183); this imbalance was communicated in the Fact Sheets. The safety database for the original EUA included data from 4220 subjects who received the 300 mg IM EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose: 3461 subjects from PROVENT, 749 subjects from STORM CHASER (the Phase 3 trial evaluating EVUSHELD for post-exposure prophylaxis), and 10 subjects from D8850C00001 (the Phase 1, first-in-human, single ascending dose study in healthy adults).

Available safety data for EVUSHELD doses higher than 300 mg IM (150 mg of tixagevimab and 150 mg of cilgavimab) include safety data from 494 subjects who received ≥600 mg EVUSHELD in the following clinical trials:

1. TACKLE (n=452 randomized to EVUSHELD), the Phase 3 trial evaluating 600 mg IM EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) for treatment of mild-to-moderate COVID-19
2. D8850C00001 (n=10 randomized to EVUSHELD 1000 mg IV, and n=20 randomized to EVUSHELD 3000 mg IV)
3. D8850C00005 (n=6 randomized to EVUSHELD 600 mg IM, and n=6 randomized to EVUSHELD 1000 mg IV), the Phase 1 dose-ranging study in healthy Japanese adults

These safety data support the use of the 600 mg IM EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose, but the number of dosed subjects is too small to support doses higher than 600 mg IM (only 36 subjects received >600 mg EVUSHELD across studies). No dose-related safety trends were evident in the two dose-ranging studies. In the Phase 3 trial TACKLE, overall safety was similar between 600 mg IM EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) and placebo recipients. A slight imbalance was noted in the number of myocardial infarction SAEs in TACKLE, with (b) (6) EVUSHELD recipients reporting acute myocardial infarctions (b) (6) and (b) (6) placebo recipients reporting myocardial infarctions. However, the cardiac SAE data from TACKLE were reviewed as part of the original EUA and were factored into the decision to communicate the imbalance in cardiovascular SAEs as a Warning and Precaution in the Fact Sheet for Healthcare Providers.

Phase 1 Dose-Ranging Studies D8850C00001 and D8850C00005:

There were no dose-related increases in overall adverse events (AEs) or specific AEs and no concerning safety findings in either D8850C00001 (which evaluated doses up to 3000 mg IV) or D8850C00005 (which evaluated doses up to 1000 mg IV). The D8850C00001 safety data were reviewed with the original EUA request. In D8850C00005, 40 Japanese adults were randomized to receive single doses of placebo (n=10), EVUSHELD 300 mg IM (n=6), EVUSHELD 600 mg IM (n=6), EVUSHELD 300 mg

IV (n=12), or EVUSHELD 1000 mg IV (n=6). Up to 30 days post-dose, there were no SAEs or severe AEs, and the only AE reported in [redacted] recipients was mild headache (reported by [redacted]).

The Phase 3 Treatment Study TACKLE

TACKLE was a Phase 3, double-blind, multicountry, multicenter study in which 903 adults with mild to moderate COVID-19 who were within 7 days of symptom onset were randomized 1:1 to either EVUSHELD 600 mg IM (300 mg of tixagevimab and 300 mg of cilgavimab) or placebo. About 90% of the study population had risk factors that put them at high risk for progression to severe COVID-19. The median follow-up at the time of the database lock was 84 days (range 1 to 177 days).

Overall safety findings in TACKLE are shown in *Table 3*. In general, rates of overall safety events were similar between treatment groups, with numerically more overall AEs, grade 3 or higher AEs, and SAEs reported in the placebo group. The only individual AE reported in ≥3% of study subjects was COVID-19 pneumonia (26, or 6%, of EVUSHELD recipients versus 49, or 11%, of placebo recipients). The only individual AEs that were reported in ≥1% of EVUSHELD recipients with a higher frequency (≥5 subject difference) versus placebo were insomnia ([redacted] EVUSHELD recipients versus [redacted] placebo recipient) and mild dizziness ([redacted] EVUSHELD recipients versus [redacted] placebo recipient); the insomnia was reported as mild in [redacted] EVUSHELD recipients and as moderate in [redacted] EVUSHELD and [redacted] placebo recipient. Notably, adverse events of special interest (injection site reactions and anaphylaxis and other serious hypersensitivity reactions) were reported by the same number of EVUSHELD and placebo recipients (15 of each).

Table 3: Summary of Safety in TACKLE

	EVUSHELD 600 mg IM (n=452)	**Placebo (n=451)**
Any AE	132 (29%)	163 (36%)
AE related to study treatment	23 (5%)	21 (5%)
Any Grade 3 or higher AE	27 (6%)	43 (10%)
SAE	33 (7%)	54 (12%)
SAE related to study treatment	0	0
AEs with outcome of death	6 (1%)	6 (1%)
AEs of special interest (AESI)*	15 (3%)	15 (3%)
AESI related to study treatment	15 (3%)	15 (3%)

Source: Sponsor's 12/31/21 response to information request dated 12/21/21, Table 14.3.1

SAEs were reported at a lower frequency in the EVUSHELD versus the placebo group (7% versus 12%, respectively). The majority of the SAEs in both treatment groups were related to progression of COVID-19: 23 (5%) of EVUSHELD recipients and 47 (10%) of placebo recipients reported an SAE of COVID-19 pneumonia, and 1 (<1%) of EVUSHELD recipients and 37 (8%) of placebo recipients reported an SAE of COVID-19. The only other SAE reported by ≥2 EVUSHELD recipients was acute myocardial infarction ([redacted] EVUSHELD recipients, [redacted], versus [redacted] placebo recipients). [redacted]

[redacted] These cardiac SAEs from TACKLE were included in the cardiac SAE assessment in the original EUA review.

The same number of deaths were reported in the EVUSHELD versus the placebo group (6 subjects in each group). In the EVUSHELD group, three fatal AEs were related to COVID-19 (two COVID-19 pneumonia and one COVID-19). In addition, one fatal AE was [redacted] In the placebo group, five fatal AEs were related to COVID-19 (four COVID-19 pneumonia and one COVID-19), and one death [redacted] The individual AEs resulting in death do not raise a safety concern beyond the slight imbalance [redacted] already noted in the original EUA review.

Other Pertinent Clinical Data

[redacted]

The Sponsor also submitted additional immunogenicity data (anti-drug antibody [ADA] assay results from 1136 subjects in PROVENT as well as results from 2 subjects in STORM CHASER and 8 subjects in TACKLE who reported thrombotic SAEs). Among the subjects evaluated in PROVENT, the prevalence of treatment-emergent ADA against either antibody in EVUSHELD over 182 days was low and was similar between the EVUSHELD and the placebo groups. A total of 10/743 (1.3%) EVUSHELD recipients and 3/393 (0.8%) placebo recipients had samples positive for ADA post-baseline who did not already have samples positive for ADA at baseline. Overall (including baseline samples), a total of 37/743 (5.0%) EVUSHELD recipients versus 14/393 (3.6%) placebo recipients had any samples positive for ADA. Among the subjects with thrombotic SAEs, there was no signal of an association with ADA positivity (only two subjects with thrombotic SAEs in this cohort had samples positive for ADA, and they were both [redacted] recipients). These data are reassuring in terms of the predicted safety of repeat dosing.

Revisions to the EUA Fact Sheets

The totality of data support changing the EVUSHELD dosing regimen to an initial EVUSHELD dose of 600 mg IM (300 mg tixagevimab and 300 mg cilgavimab) and to remove the repeat dosing recommendations until more data on the variants that may be circulating in 3-6 months, and their susceptibility to EVUSHELD, are available. The safety data from TACKLE after a single EVUSHELD 600 mg IM (300 mg tixagevimab and 300 mg cilgavimab) dose support this increased dose. Pharmacokinetic and pharmacodynamic modeling using the EVUSHELD neutralization data against the Omicron subvariants BA.1 and BA.1.1 suggest that the EVUSHELD 300 mg IM (150 mg tixagevimab and 150 mg cilgavimab) every 6 months regimen that was initially authorized may not be sufficient to provide protection; however, the modeling suggests in vivo activity against these subvariants may be retained for up to 3 months at drug concentrations achieved following a single EVUSHELD initial dose of 600 mg IM (300 mg tixagevimab and 300 mg cilgavimab).

The following sections of the EUA Fact Sheet for Healthcare Providers have been updated to incorporate these changes to the dosing regimen; please see the revised Fact Sheet for Healthcare Providers for full details.

- Section 2.1 Dosage for Emergency Use of EVUSHELD: The revisions specify the following:
    - Due to decreased neutralization activity of EVUSHELD against the Omicron subvariants BA.1 and BA.1.1, the initial dose is 300 mg of tixagevimab and 300 mg of cilgavimab.
    - Due to the likely reduced duration of protection against the Omicron subvariants BA.1 and BA.1.1, the repeat dosing recommendations have been removed and these recommendations will be updated when more data are available.
    - Individuals who have already received the previously authorized EVUSHELD 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.
    - EVUSHELD has only been studied for the prophylaxis of COVID-19 at the 150 mg tixagevimab and 150 mg cilgavimab dose, and there are no safety or efficacy data available with repeat dosing.
    - The dosing recommendations are based on the totality of scientific evidence including clinical pharmacology data, antiviral activity data, and clinical trial data.
- Section 2.3 Dose Preparation and Administration: The revisions specify the following:
    - The number of vials needed and volume to withdraw from the vials for each antibody for each EVUSHELD dose.
    - That location of EVUSHELD administration for initial dosing should be a muscle that can accommodate the higher 3 mL volume of each injection (e.g., the gluteal muscles).

- Section 6.1 Adverse Reactions from Clinical Studies was updated with safety data with the 300 mg tixagevimab and 300 mg cilgavimab dose from TACKLE.
- Section 6.4 was revised, and Section 6.5 was added, to update safety reporting information for consistency with other EUA Fact Sheets.
- Section 8.5 Geriatric Use was updated with safety and PK information from geriatric subjects in TACKLE.
- Section 12.3 Pharmacokinetics was updated with PK information for the 300 mg tixagevimab and 300 mg cilgavimab dose as well as PK modeling to support the new initial dose.
- Section 12.4 Microbiology was updated with the most recent data on the neutralizing activity of EVUSHELD against different variants (including the Omicron subvariants BA.1.1 and BA.2 as well as C.36.3, B.1.214.2, B.1.619.1, and P.2).
- Section 17 Patient Counseling Information was updated with counseling information related to the new dosing recommendations.

The Fact Sheet for Patients, Parents and Caregivers was also updated to specify that additional doses of EVUSHELD may be needed but that the best timing is not known right now.

II. Regulatory Conclusions

Given the totality of evidence, it has been determined that Section 2 on Dosage and Administration should be modified to increase EVUSHELD exposures in response to reduced activity against Omicron BA.1 and BA.1.1. The new authorized initial dose of EVUSHELD is 600 mg IM (300 mg tixagevimab and 300 mg cilgavimab). This new dosing regimen was chosen based on the neutralization activity of EVUSHELD against the Omicron BA.1 and BA.1.1 variants, PK modeling, and the maximum exposures supported by clinical safety data from the Phase 3 trial TACKLE. In addition, Section 6 on Adverse Reactions has been updated to add the safety data from TACKLE that support the EVUSHELD 600 mg IM (300 mg tixagevimab and 300 mg cilgavimab) dose, Section 8.5 on Geriatric Use was updated with additional PK data from TACKLE, Section 12.3 on Pharmacokinetics was updated with additional PK data to support the new dose, Section 12.4 on Microbiology was updated with the most recent data on the neutralizing activity of EVUSHELD against different variants, and Section 17 was updated with new patient counseling information related to the new dosing recommendations. The revisions to the EUA Fact Sheet for Health Care Providers were made in order to minimize the risk of product failure and to provide health care providers with the most current information as to the recommended dosing regimen. Collectively, the revisions to the Fact Sheets detailed above do not alter the analysis of benefits and risks that underlies the initial authorization of EUA 104.

To obtain more information on the safety of repeat dosing at these higher doses and to obtain safety and PK data to support higher doses if those are needed in in the setting of future emerging SARS-CoV-2 variants, we are also amending the letter of authorization to add the following condition of authorization:

- AstraZeneca must conduct an additional randomized, dose-ranging clinical trial in the target population (individuals with moderate to severe immunocompromise who may not mount an adequate immune response to COVID-19 vaccination) evaluating the following dosing regimens for COVID-19 pre-exposure prophylaxis:

- EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) administered as two consecutive IM injections followed 3 months later by EVUSHELD (150 mg tixagevimab and 150 mg cilgavimab) administered as two consecutive IM injections with subsequent redosing every 3 months.
- EVUSHELD (600 mg tixagevimab and 600 mg cilgavimab) administered as an intravenous infusion followed 6 months later by EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) administered as two consecutive IM injections with subsequent redosing every 6 months.

At least 100 subjects should be randomized to each dosing regimen. The primary objectives of the trial would be to evaluate safety and immunogenicity, but pharmacokinetic, pharmacodynamic, and efficacy data should also be collected. AstraZeneca must provide the Agency with a protocol for this trial no later than February 28, 2022.

References

1. Magyarics Z, Leslie F, Bartko J, et al. Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study of the Penetration of a Monoclonal Antibody Combination (ASN100) Targeting Staphylococcus aureus Cytotoxins in the Lung Epithelial Lining Fluid of Healthy Volunteers. Antimicrob Agents Chemother 2019; 63(8).

2. Chigutsa E, Jordie E, Riggs M, et al. A Quantitative Modeling and Simulation Framework to Support Candidate and Dose Selection of Anti-SARS-CoV-2 Monoclonal Antibodies to Advance Bamlanivimab Into a First-in-Human Clinical Trial. Clin Pharmacol Ther 2022; 111(3): 595-604.

3. Chigutsa E, O'Brien L, Ferguson-Sells L, Long A, Chien J. Population Pharmacokinetics and Pharmacodynamics of the Neutralizing Antibodies Bamlanivimab and Etesevimab in Patients With Mild to Moderate COVID-19 Infection. Clin Pharmacol Ther 2021; 110(5): 1302-10.

4. Jones BE, Brown-Augsburger PL, Corbett KS, et al. The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates. Sci Transl Med 2021; 13(593).

5. Jadhav SB, Khaowroongrueng V, Fueth M, Otteneder MB, Richter W, Derendorf H. Tissue Distribution of a Therapeutic Monoclonal Antibody Determined by Large Pore Microdialysis. J Pharm Sci 2017; 106(9): 2853-9.

6. Shah DK, Betts AM. Antibody biodistribution coefficients: inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. MAbs 2013; 5(2): 297-305.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use EVUSHELD™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for EVUSHELD.

EVUSHELD (tixagevimab) injection; (cilgavimab) injection, co-packaged for intramuscular use
Original EUA Authorized Date: 12/2021

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1, 17): modification of initial dosage and repeat dosing	02/2022
Adverse Reactions (6.1, 12.3): addition of TACKLE data	02/2022
Microbiology (12.4): updated neutralizing data	02/2022

----------EUA FOR EVUSHELD----------

The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab), SARS-CoV-2 spike protein-directed attachment inhibitor, 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):

- 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).

EVUSHELD may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which EVUSHELD belongs (i.e., anti-infectives).

EVUSHELD has been authorized by FDA for the emergency use descr bed above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19. (1)

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - o For treatment of COVID-19, or
  - o For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

See Full Fact Sheet for Healthcare Providers for examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination, the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19. (1)

----------DOSAGE AND ADMINISTRATION----------

The dosage of EVUSHELD for emergency use is:

- Initial dose: 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections.
- Repeat dose: The SARS-CoV-2 variants that will be circulating in the United States when EVUSHELD may need to be redosed are not known at this time and therefore repeat dosing recommendations cannot be made; the Fact Sheets will be revised with repeat dosing recommendations in the future when more data are available. (2.1)

See Full Fact Sheet for Healthcare Providers for detail on preparation and administration. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection:

- tixagevimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)
- cilgavimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of EVUSHELD. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Including Anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, have been observed with IgG1 monoclonal antibodies l ke EVUSHELD. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Clinically monitor individuals after injections and observe for at least 1 hour. (5.1)
- Clinically Significant Bleeding Disorders: As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder. (5.2)
- Cardiovascular Events: A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events. All of the subjects with 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. 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. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse events (all grades, incidence ≥3%) are headache, fatigue, and cough. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to EVUSHELD (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to *AstraZeneca* by Fax at 1-866-742-7984 or call 1-800-236-9933. (6.4)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

Revised 02/2022

TABLE OF CONTENTS*

* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab) 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):

- 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[1] **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).

EVUSHELD may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which EVUSHELD belongs (i.e., anti-infectives).

EVUSHELD has been authorized by FDA for the emergency use described above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

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[1]:

- 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)
- 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)

[1] For additional information please see https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Healthcare providers should consider the benefit-risk for an individual patient.

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
  - The product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
  - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There are no adequate, approved and available alternatives to EVUSHELD for the pre-exposure prophylaxis of COVID-19 in individuals who may not mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components.

For information on clinical studies of EVUSHELD and other therapies for the prophylaxis of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of EVUSHELD

Initial Dosing

Due to decreased neutralization activity of EVUSHELD against the Omicron subvariants BA.1 and BA.1.1 (BA.1+R346K), the initial dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered as two separate consecutive intramuscular (IM) injections *[see Clinical Pharmacology (12.3)]*. Refer to Table 1 below.

Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg of Cilgavimab

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**. Any subsequent repeat dosing should be timed from the date of the second EVUSHELD dose. Refer to Table 2 below.

Repeat Dosing

EVUSHELD has only been studied in single-dose studies. There are no safety and efficacy data available with repeat dosing. Longer term data from the study PROVENT indicated that EVUSHELD may be effective for pre-exposure prophylaxis for 6 months post-administration for pre-Omicron SARS-CoV-2 variants *[see Clinical Studies (14)]*. However, the neutralization activity of EVUSHELD against the Omicron subvariants (BA.1, and BA.1.1 [BA.1+R346K]) versus the reference strain decreases 12- to 424-fold *[see Microbiology (12.4)]*, and consequently the duration of protection is not known and is likely reduced. Conversely, the neutralization activity of EVUSHELD against the Omicron BA.2 subvariant versus the reference strain is minimally impacted *[see Microbiology (12.4)]*.

Because it is unclear which SARS-CoV-2 variant or Omicron subvariant will become dominant in the United States over the next few months, **the recommended timing for repeat dosing cannot be provided at this time**. The Fact Sheets will be revised with repeat dosing recommendations in the near future when more data are available to determine the appropriate timing of redosing (e.g., a repeat dose with 150 mg of tixagevimab and 150 mg of cilgavimab 3 months or 6 months after the prior dose).

To access the most recent EVUSHELD Fact Sheets, please visit http://www.evusheld.com or scan the QR code:

The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical trial data *[see Clinical Pharmacology (12.3), Microbiology (12.4), and Clinical Studies (14)]*. EVUSHELD has only been studied for the prophylaxis of COVID-19 at the EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose. There are no data available in a prophylaxis setting for the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose. The clinical safety of the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose is supported by safety data from a treatment study in subjects with mild to moderate COVID-19 *[see Adverse Reactions (6.1)]*.

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, and in individuals with renal impairment *[see Use in Specific Populations (8)]*.

2.3 Dose Preparation and Administration

Each EVUSHELD carton contains two vials; one of each antibody. Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

Table 1 Initial Dosage of 300 mg of Tixagevimab and 300 mg of Cilgavimab

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial(s)
	tixagevimab 300 mg	2 vials	3 mL
	cilgavimab 300 mg	2 vials	3 mL

* 300 mg of tixagevimab and 300 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

Table 2 Dosage of 150 mg of Tixagevimab and 150 mg of Cilgavimab^

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial
	tixagevimab 150 mg	1 vial	1.5 mL
	cilgavimab 150 mg	1 vial	1.5 mL

* 150 mg of tixagevimab and 150 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

^ Dosing for individuals who initially received 150 mg of tixagevimab and 150 mg of cilgavimab

Preparation

- Tixagevimab and cilgavimab must be prepared by a qualified healthcare provider.
- Tixagevimab and cilgavimab are each supplied in individual single-dose vials. Do not shake the vials.
- Visually inspect the vials for particulate matter and discoloration. Tixagevimab and cilgavimab are clear to opalescent, colorless to slightly yellow solutions. Discard the vials if the solution is cloudy, discolored or visible particles are observed.
- Administer EVUSHELD as TWO separate, consecutive intramuscular (IM) injections, 1 injection of tixagevimab and 1 injection of cilgavimab.
- Withdraw the appropriate amount of tixagevimab solution and the appropriate amount of cilgavimab solution into TWO separate syringes (see Table 1 and Table 2). Discard unused portion in vials.
- This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, and the prepared tixagevimab and

cilgavimab syringes need to be stored, the total time from vial puncture to administration must not exceed 4 hours:
    - in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF), or
    - at room temperature up to 25ºC (77ºF).

Administration

- Tixagevimab and cilgavimab must be administered by a qualified healthcare provider.
- Administer the two components of EVUSHELD consecutively.
- Administer the IM injections at different injection sites, preferably one in each of the gluteal muscles, one after the other.
    - For the 300 mg tixagevimab and 300 mg cilgavimab dose, ensure that the administration sites are appropriate for the volume (3 mL per injection).
- Clinically monitor individuals after injections and observe for at least 1 hour *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

EVUSHELD is available as an individual single-dose vial of tixagevimab as a clear to opalescent, colorless to slightly yellow solution co-packaged with an individual single-dose vial of cilgavimab as a clear to opalescent, colorless to slightly yellow solution as:

- Injection: 150 mg/1.5 mL (100 mg/mL) of tixagevimab
- Injection: 150 mg/1.5 mL (100 mg/mL) of cilgavimab

4 CONTRAINDICATIONS

EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of EVUSHELD *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for EVUSHELD. Serious and unexpected adverse events may occur that have not been previously reported with EVUSHELD use.

5.1 Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with Human immunoglobulin G1 (IgG1) monoclonal antibodies like EVUSHELD *[see Adverse Reactions (6.1)]*. 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.

5.2 Clinically Significant Bleeding Disorders

As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder.

5.3 Cardiovascular Events

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 *[see Adverse Reactions (6.1)]*. All subjects who experienced cardiac SAEs 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. There was no signal for cardiac toxicity or thrombotic events identified in the nonclinical studies.

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.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse events have been observed in the clinical studies of EVUSHELD that supported the EUA. The adverse event rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse events associated with EVUSHELD may become apparent with more widespread use.

Approximately 4,220 subjects have been exposed to EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) in two ongoing Phase III trials, PROVENT and STORM CHASER, for the prophylaxis of COVID-19. The primary safety analysis was based on data through to event driven efficacy data cut-offs, such that individual subjects had variable follow-up times *[see Clinical Studies (14)]*, with a median (range) of follow-up of 83 days (3-166 days) for PROVENT and 49 days (5-115 days) for STORM CHASER. An additional data cut-off was conducted to provide updated analyses with a median (range) of follow-up of 6.5 months (3-282 days) for PROVENT and approximately 6 months (5-249 days) for STORM CHASER. The median and range of follow-up times were similar between EVUSHELD and placebo recipients in each trial.

Four hundred and fifty two (452) non-hospitalized subjects (with the exception of those hospitalized for isolation purposes) with mild to moderate COVID-19 have been exposed to EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) in one ongoing Phase III clinical trial, TACKLE. The median (range) duration of follow-up was 84 days (1-183 days). EVUSHELD is not authorized for treatment of COVID-19 *[see Limitations of Authorized Use (1)]*.

In all studies, adults received EVUSHELD administered as two separate, consecutive IM injections of tixagevimab and cilgavimab or placebo *[see Clinical Studies (14)]*.

PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg of cilgavimab])
PROVENT enrolled adults ≥18 years of age who were either ≥60 years of age, had pre-specified co-morbidities *[see Clinical Studies (14)]*, or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine or have known prior or current SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 3,461) or placebo (N= 1,736).

Adverse events were reported in 1,221 (35%) subjects receiving EVUSHELD and 593 (34%) receiving placebo. SAEs were reported in 50 (1%) subjects receiving EVUSHELD and 23 (1%) receiving placebo. There was 1 adverse event reported as anaphylaxis among subjects who received EVUSHELD. The event began within minutes of EVUSHELD administration and was treated with epinephrine. The event resolved.

Of the reported adverse events (N= 4,507), the majority were mild (73%) or moderate (24%) in severity. All adverse events, occurring in at least 1% of subjects, were reported at similar incidence rates among subjects receiving EVUSHELD compared to those receiving placebo (difference <1%). The most common treatment-emergent adverse events, occurring in at least 3% of subjects receiving EVUSHELD or placebo are shown in Table 3.

Table 3 Adverse Events (All Grades) Regardless of Causality Occurring in at Least 3% of Subjects Receiving EVUSHELD or Placebo in Primary Safety Analysis

	EVUSHELD N= 3,461	**Placebo N= 1,736**
Headache	6%	5%
Fatigue	4%	3%
Cough	3%	3%

At the additional data cut-off (median follow-up 6.5 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to events displayed in Table 3.

Cardiac Serious Adverse Events
Through the additional data cut-off in PROVENT, a higher proportion of subjects who received EVUSHELD versus placebo in PROVENT reported myocardial infarction SAEs, one of which resulted in death, and cardiac failure SAEs (see Table 4 below). All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline. There was no clear temporal pattern, with events reported from several hours after EVUSHELD receipt through the end of the follow-up period.

Table 4 Cardiac SAEs Regardless of Causality in PROVENT with Onset Prior to Day 183 Using the Median 6-Month Data Cut-off Date

	EVUSHELD N= 3,461	**Placebo N= 1,736**
Subjects with any cardiac SAE*	22 (0.6%)	3 (0.2%)
SAEs related to coronary artery disease or myocardial ischemia†	10 (0.3%)	2 (0.1%)
Myocardial infarctions‡	8 (0.2%)	1 (0.1%)
SAEs related to cardiac failure§	6 (0.2%)	1 (0.1%)
SAEs related to an arrhythmia¶	4 (0.1%)	1 (0.1%)
Other (cardiomegaly, cardiomyopathy, and cardio-respiratory arrest)	3 (0.1%)	0

* One EVUSHELD recipient and one placebo recipient had two cardiac SAEs each.
† Includes the preferred terms angina pectoris, coronary artery disease, arteriosclerosis, troponin increased, acute myocardial infarction, and myocardial infarction.
‡ Includes the preferred terms acute myocardial infarction, myocardial infarction, and troponin increased (with a discharge diagnosis of myocardial infarction).
§ Includes the preferred terms cardiac failure congestive, acute left ventricular failure, cardiac failure, and cardiac failure acute.
¶ Includes the preferred terms atrial fibrillation, arrhythmia, paroxysmal atrioventricular block, and heart rate irregular.

STORM CHASER (EVUSHELD [150 mg tixagevimab and 150 mg cilgavimab])
STORM CHASER enrolled adults ≥18 years of age following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects could not have previously received a COVID-19 vaccine, have symptoms consistent with COVID-19, or have a known prior SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 749) or placebo (N= 372).

Adverse events were reported in 162 (22%) subjects receiving EVUSHELD and 111 (30%) receiving placebo. SAEs were reported in 5 (<1%) subjects receiving EVUSHELD and 3 (<1%) receiving placebo. Of the reported adverse events (N= 777), the majority were mild (75%) or moderate (23%) in severity.

At the additional data cut-off (median follow-up approximately 6 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to earlier results. EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2 *[see Emergency Use Authorization (1)]*.

Cardiac Serious Adverse Events
In STORM CHASER (N= 1,121) no cardiac SAEs were reported (median follow-up approximately 6 months). Compared to PROVENT, the subjects in STORM CHASER were younger (median age 48 versus 57 years) and had fewer baseline cardiac risk factors (24% versus 36% with hypertension, 11% versus 14% with diabetes, and 3% versus 8% with cardiovascular disease in STORM CHASER versus PROVENT, respectively).

TACKLE (EVUSHELD [300 mg tixagevimab and 300 mg cilgavimab])
TACKLE enrolled adults ≥18 years of age with mild to moderate COVID-19 who were within ≤7 days of symptom onset. Approximately 90% of study subjects had risk factors that put them at high risk for progression to severe COVID-19. Subjects received a single dose of EVUSHELD (N= 452) or placebo (N= 451).

Adverse events were reported in 132 (29%) subjects receiving EVUSHELD and 163 (36%) receiving placebo. Serious adverse events were reported in 33 (7%) subjects receiving EVUSHELD and 54 (12%) receiving placebo. Of the reported adverse events (N= 520), the majority were mild (56%) or moderate (27%) in severity. There were no reports of anaphylaxis or serious hypersensitivity reactions.

Adverse events of insomnia (1% vs. <1%) and dizziness (1% vs. none) were reported at a higher rate with EVUSHELD compared to placebo. No other treatment-emergent adverse events, occurring in at least 1% of subjects, were reported at higher incidence rates (difference ≥1%) among subjects receiving EVUSHELD compared to those receiving placebo.

Cardiac Serious Adverse Events
In TACKLE (N= 903) four subjects reported cardiac SAEs. Acute myocardial infarction was reported for two subjects who received EVUSHELD (one of whom also experienced cardiac failure leading to death) and sudden cardiac death was reported for one subject who received EVUSHELD. One subject who received placebo reported arrhythmia. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

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 within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "EVUSHELD use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to AstraZeneca:

- Fax 1-866-742-7984

and to report adverse events please:

- Visit https://contactazmedical.astrazeneca.com, or
- Call AstraZeneca at 1-800-236-9933.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of EVUSHELD.

*Serious adverse events are defined as:

- Death
- a life-threatening adverse event;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;

- Inpatient hospitalization or prolongation of existing hospitalization.

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS

Drug-drug interaction studies have not been performed.

Tixagevimab and cilgavimab are not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with tixagevimab and cilgavimab. In a tissue cross-reactivity study assessing off-target binding of tixagevimab and cilgavimab to human fetal tissues no binding of clinical concern was observed. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, tixagevimab and cilgavimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of tixagevimab and cilgavimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary
There are no available data on the presence of tixagevimab or cilgavimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVUSHELD and any potential adverse effects on the breastfed infant from EVUSHELD.

8.4 Pediatric Use

EVUSHELD is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of EVUSHELD have not been established in pediatric individuals. The dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the trials PROVENT, STORM CHASER and TACKLE *[see Adverse Reactions (6.1) and Clinical Studies (14)].*

8.5 Geriatric Use

Of the 2,555 subjects in the pooled pharmacokinetics (PK) analysis (Phase I and Phase III studies), 21% (N= 533) were 65 years of age or older and 3% (N= 81) were 75 years of age or older. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger subjects.

8.6 Renal Impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine, renal impairment is not expected to affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

8.7 Hepatic Impairment

The effect of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

8.8 Other Specific Populations

Based on a population PK analysis, the PK profile of tixagevimab and cilgavimab was not affected by sex, age, race, or ethnicity. Population PK model-based simulations suggest that body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in healthy adults over the range of 36 kg to 177 kg.

10 OVERDOSAGE

Treatment of overdose with EVUSHELD should consist of general supportive measures including the monitoring of the clinical status of the individual. There is no specific treatment for overdose with EVUSHELD.

11 DESCRIPTION

Tixagevimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human immunoglobulin G1 (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The molecular weight is approximately 149 kDa.

Tixagevimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg tixagevimab, L- histidine (2.4 mg), L- histidine

hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

Cilgavimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human IgG1κ monoclonal antibody produced in CHO cells by recombinant DNA technology. The molecular weight is approximately 152 kDa.

Cilgavimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg cilgavimab, L- histidine (2.4 mg), L- histidine hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies with amino acid substitutions to extend antibody half-life (YTE), reduce antibody effector function, and minimize the potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the receptor binding domain (RBD) of SARS-CoV-2 spike protein. Tixagevimab, cilgavimab, and their combination bind to spike protein with equilibrium dissociation constants of K_D = 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with human ACE2, the SARS-CoV-2 receptor, which is required for virus attachment. Tixagevimab, cilgavimab, and their combination blocked RBD binding to human ACE2 with IC_{50} values of 0.32 nM (48 ng/mL), 0.53 nM (80 ng/mL), and 0.43 nM (65 ng/mL), respectively.

12.3 Pharmacokinetics

A summary of PK parameters and properties of tixagevimab and cilgavimab following administration of a single EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) intramuscular dose is provided in Table 5.

Table 5 Summary of PK Parameters and Properties of Tixagevimab and Cilgavimab Following a Single EVUSHELD (300 mg Tixagevimab and 300 mg Cilgavimab) Intramuscular Dose

PK Parameters	Tixagevimab	Cilgavimab
C_{max} (µg/mL)*	21.9 (61.7)	20.3 (63.6)
T_{max} (day)†	14.9 (1.1 – 86)	15.0 (1.1 – 85)
C_2 (µg/mL)‡	9.5 (77)	9.1 (80)
C_{84} (µg/mL)§	15 (48)	14 (51)
AUC_{0-84} (day•µg/mL)*	1408 (54)	1307 (58)
Absorption		
Bioavailability#¶	68.5	65.8
Distribution		
Apparent Volume of Distribution (L)#	7.7 (1.97)	8.7 (2.73)
Elimination		
Half-life (days)#¶	87.9 (13.9)	82.9 (12.3)

PK Parameters	Tixagevimab	Cilgavimab
Apparent Clearance (L/day)[#]	0.062 (0.019)	0.074 (0.028)
Metabolism	Catabolic pathways; Same manner as endogenous IgG	
Excretion	Not likely to undergo renal excretion	

* Geomean (geometric %CV)
† Median (range)
‡ Observed geomean (geometric %CV) concentration 2 day after dosing
§ Observed geomean (geometric %CV) concentration 84 days after dosing
# Arithmetic mean (SD)
¶ Based on a single EVUSHELD (150 mg tixagevimab and 150 mg cilgavimab)

The primary analysis in the clinical efficacy study PROVENT was conducted prior to the emergence of the Omicron variant; the dominant variants in circulation at that time were Alpha, Beta, Gamma, and Delta. Pharmacokinetic and pharmacodynamic modeling using cell-based EC_{50} values of EVUSHELD against Omicron subvariants (BA.1 and, BA.1.1 [BA.1+R346K]) suggest in vivo activity against these subvariants may be retained at drug concentrations achieved following a single EVUSHELD initial dose of 300 mg tixagevimab and 300 mg cilgavimab for 3 months *[see Dosage and Administration (2.1)]*.

Specific Populations

The PK profile of tixagevimab and cilgavimab were not affected by sex, age, race or ethnicity. Body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in adults over the range of 36 kg to 177 kg.

Pediatric Population

The PK of tixagevimab and cilgavimab in pediatric individuals have not been evaluated.

The dosing regimen is expected to result in comparable plasma exposures of tixagevimab and cilgavimab in pediatric individuals ages 12 years of age or older who weigh at least 40 kg as observed in adult individuals *[see Use in Specific Populations (8.4)]*.

Renal impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine.

Renal impairment is not expected to impact the PK of tixagevimab and cilgavimab, since monoclonal antibodies with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

There is no difference in the clearance of tixagevimab and cilgavimab in individuals with mild or moderate renal impairment compared to individuals with normal renal function. There were insufficient subjects with severe renal impairment to draw conclusions *[see Use in Specific Populations (8.6)]*.

Hepatic impairment

No specific studies have been conducted to examine the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies
Drug-drug interaction studies have not been performed. Based on key elimination pathways, tixagevimab and cilgavimab interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Drug Interactions (7)]*.

12.4 Microbiology

Antiviral Activity
In a neutralization assay on Vero E6 cells, tixagevimab, cilgavimab, and their combination neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 60.7 pM (9 ng/mL), 211.5 pM (32 ng/mL), and 65.9 pM (10 ng/mL), respectively.

Tixagevimab, cilgavimab, and their combination showed reduced or no antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or antibody-dependent natural killer cell activation (ADNKA) in cell culture studies. Tixagevimab, cilgavimab, and their combination did not mediate antibody-dependent complement deposition (ADCD) activity with guinea pig complement proteins.

Antibody Dependent Enhancement (ADE) of Infection
The potential of tixagevimab and cilgavimab to mediate antibody-dependent viral entry was assessed in FcγRII-expressing Raji cells co-incubated with recombinant virus-like particles (VLPs) pseudotyped with SARS-CoV-2 spike protein, with antibody concentrations at a range of 6.6 nM (1 µg/mL) to 824 pM (125 ng/mL). Tixagevimab, cilgavimab, and their combination did not mediate entry of VLPs into these cells under the tested conditions.

The potential for ADE was also evaluated in a non-human primate model of SARS-CoV-2 using EVUSHELD. Intravascular administration prior to virus inoculation resulted in a dose-dependent improvement in all measured outcomes (total viral RNA in the lungs or nasal mucosae, infectious virus levels in the lungs based on $TCID_{50}$ measurements, or lung injury and pathology based on histology measurements). No evidence of enhancement of viral replication or disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.04 mg/kg.

Antiviral Resistance
There is a potential risk of treatment failure due to the development of viral variants that are resistant to tixagevimab and cilgavimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering prophylactic treatment options.

Escape variants were identified following serial passage in cell culture of SARS-CoV-2 or replication competent recombinant vesicular stomatitis virus (VSV) expressing SARS-CoV-2 spike protein in the presence of tixagevimab or cilgavimab individually or in combination. Variants which showed reduced susceptibility to cilgavimab expressed spike protein amino acid substitutions R346I (>200-fold), K444E (>200-fold), and K444R (>200-fold). No escape variants to tixagevimab, or the tixagevimab and cilgavimab combination were selected.

In neutralization assays using recombinant VLPs pseudotyped with SARS-CoV-2 spike and harboring individual spike amino acid substitutions identified in circulating SARS-CoV-2, variants with reduced susceptibility to cilgavimab alone included those with R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold), K444R (>200-fold), V445A (21- to 51-fold), G446V (4.2-fold), N450K (9.1-fold), or L452R

(5.8-fold) substitutions. Variants with reduced susceptibility to tixagevimab alone included those with Q414R (4.6-fold), L455F (2.5- to 4.7-fold), G476S (3.3-fold), E484D (7.1-fold), E484K (6.2- to 12-fold), E484Q (3.0-fold), F486S (>600-fold), F486V (121- to 149-fold), Q493K (2.4- to 3.2-fold), Q493R (7.9-fold), E990A (6.1-fold), or T1009I (8.2-fold) substitutions. Variants harboring an E484K (2.4- to 5.4-fold), Q493R (3.4-fold), E990A (5.7-fold), or T1009I (4.5-fold) substitution exhibited low level reduced susceptibility to tixagevimab and cilgavimab in combination.

VLPs pseudotyped with the SARS-CoV-2 spike of variant strains with reduced susceptibility to cilgavimab included those with R346K:E484K:N501Y (Mu, 21-fold), and those with reduced susceptibility to tixagevimab included those harboring E484K (Alpha, 18.5-fold; Beta, 3.5- to 15-fold; Zeta, 7.3-fold). Similar results were observed, where data was available, in neutralization assays using authentic SARS-CoV-2 variant strains.

VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced susceptibility to tixagevimab (>600- to >1,000-fold or 460-fold, respectively) and to cilgavimab (>700- to >1,000-fold or >500-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.2 showed reduced susceptibility to tixagevimab (>1,000-fold) but not to cilgavimab (1.9-fold). The effects of the individual substitutions in Omicron spike glycoproteins on neutralization susceptibility are being investigated.

The neutralizing activity of tixagevimab and cilgavimab in combination was tested against pseudotyped VLPs and/or authentic SARS-CoV-2 variant strains harboring all spike substitutions identified in Alpha (B.1.1.7, 0.5- to 5.2-fold), Beta (B.1.351, 1.0- to 3.8-fold), Gamma (P.1, 0.4- to 2.0-fold), Delta (B.1.617.2, 0.6- to 1.2-fold), and Delta [+K417N] (AY.1/ AY.2, 1.0-fold) variants of concern, and Eta (B.1.525, 3.1-fold), Iota (B.1.526, 0.3- to 3.4-fold), Kappa (B.1.617.1, 0.5- to 3.4-fold) Lambda (C.37, 0.7-fold), and Mu (B.1.621, 7.5-fold) variants of interest. Tixagevimab and cilgavimab in combination was also tested against Epsilon (B.1.427 / B.1.429, 0.8- to 3.5-fold), R.1 (3.5-fold), B.1.1.519 (1.4-fold), C.36.3 (2.3-fold), B.1.214.2 (0.8-fold), and B.1.619.1 (3.3-fold) variant alerts for further monitoring and B.1.616 (0.5-fold), A.23.1 (0.4-fold), A.27 (0.8-fold), and AV.1 (5.9-fold) variants de-escalated from further monitoring (Table 6).

Preliminary data for the neutralizing activities of tixagevimab and cilgavimab in combination against circulating Omicron subvariants are available. VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced neutralizing activity (132- to 183-fold or 424-fold, respectively), Omicron BA.2 showed no change in neutralizing activity (3.2-fold). Authentic Omicron BA.1 (12- to 30-fold) and BA.1.1 (176-fold) viruses showed reduced susceptibility, Omicron BA.2 showed minimal change in neutralizing activity (5.4-fold).

Data collection is ongoing to better understand how the reductions in activity seen in pseudotyped VLP assays or authentic SARS-CoV-2 assays may correlate with clinical outcomes.

Table 6 EVUSHELD Pseudotyped Virus-Like Particles and Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
B.1.1.7	UK	Alpha	N501Y	0.5- to 5.2-fold	No Change§
B.1.351	South Africa	Beta	K417N+E484K+N501Y	No Change§	No Change§

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
P.1	Brazil	Gamma	K417T+E484K+N501Y	No Change§	No Change§
B.1.617.2	India	Delta	L452R+T478K	No Change§	No Change§
AY.1/ AY.2	India	Delta [+K417N]	K417N+L452R+T478K	No Change§	No Change§
BA.1	Botswana	Omicron (BA.1)	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q489R+N501Y+Y505H	132- to 183-fold#	12- to 30-fold
BA.1.1	Multiple country origin	Omicron (BA.1.1) [+R346K]	G339D+R346K+S371L+ S373P+S375F+K417N+ N440K+G446S+S477N+ T478K +E484A+Q493R +G496S+Q489R+N501Y+ Y505H	424-fold	176-fold
BA.2	Multiple country origin	Omicron (BA.2)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H+H655Y+N679K +P681H+N764K	No Change§	5.4-fold
B.1.525	Multiple country origin	Eta	E484K	No Change§	ND
B.1.526	United States	Iota	E484K	No Change§	No Change§
B.1.617.1	India	Kappa	L452R+E484Q	No Change§	No Change§
C.37	Peru	Lambda	L452Q+F490S	No Change§	ND
B.1.621	Colombia	Mu	R346K+E484K +N501Y	7.5-fold	ND
B.1.427 / B.1.429	United States	Epsilon	L452R	No Change§	No Change§
R.1	Multiple country origin	-	E484K	No Change§	ND
B.1.1.519	Multiple country origin	-	T478K	No Change§	ND
C.36.3	Multiple country origin	-	R346S:L452R	No Change§	ND
B.1.214.2	Multiple country origin	-	Q414K:N450K	No Change§	ND
B.1.619.1	Multiple country origin	-	N440K:E484K	No Change§	ND
P.2	Brazil	Zeta	E484K	No Change§	ND
B.1.616	France	-	V483A	No Change§	ND
A.23.1	UK	-	V367F	No Change§	ND
A.27	Multiple country origin	-	L452R+N501Y	No Change§	ND
AV.1	Multiple country origin	-	N439K+E484K	5.9-fold	ND

* Range of reduced potency across multiple variants of each lineage using research-grade pseudotyped VLP neutralization assays; mean fold change in half maximal effective concentration (EC_{50}) of mAb required for a 50% reduction in infection compared to wild type reference strain

† Pseudotyped virus-like particles expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions except L452Q were tested including Alpha (+L455F, E484K, F490S, Q493R, and/or S494P), and Delta (+K417N) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages
‡ Authentic SARS-CoV-2 expressing the entire variant spike protein were tested including Alpha (+E484K or S494P) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages
§ No change: <5-fold reduction in susceptibility
# EC_{50} value = 1.13 – 1.83 nM (171 - 277 ng/mL)
ND, not determined; RBD, receptor binding domain

It is not known how pseudotyped VLPs or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome.

In PROVENT, illness visit sequencing data were available for 21 of 33 subjects with SARS-CoV-2 infection (6 who received tixagevimab and cilgavimab and 15 placebo). Fourteen subjects were infected with variants of concern or variants of interest, including 8 subjects with Alpha (B.1.1.7) (8 who received placebo), 1 subject with Beta (B.1.351) (1 who received tixagevimab and cilgavimab), 3 subjects with Delta (B.1.617.2) (3 who received placebo), and 2 subjects with Epsilon (B.1.429) (2 who received tixagevimab and cilgavimab). Seven additional subjects were infected with B.1.375 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and P681H or Q677P (3 who received tixagevimab and cilgavimab and 3 placebo). Additional spike protein RBD substitutions detected at low frequency (between 3% and 24%) included V503F in the tixagevimab and cilgavimab group.

In STORM CHASER, illness visit sequencing data was available for 19 of 19 subjects with SARS-CoV-2 infections (12 of 12 who received tixagevimab and cilgavimab and 7 of 7 placebo). At an allele fraction ≥25%, 12 of 19 subjects were infected with variants of concern or variants of interest, including 9 subjects with Alpha (B.1.1.7) (5 who received tixagevimab and cilgavimab and 4 placebo) and 3 subjects with Epsilon (B.1.427 / B.1.429) (2 who received tixagevimab and cilgavimab and 1 placebo). Seven additional subjects were infected with B.1.1.519 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and D138H, Q675H, Q677H, or V1176F (4 who received tixagevimab and cilgavimab and 2 placebo). Additional spike protein RBD substitutions detected at an allele fraction ≥3% included S325P, Del342, C361W, Del428, F429V, and F515C in the tixagevimab and cilgavimab group.

Evaluation of neutralization susceptibility of variants identified through global surveillance and in subjects who received tixagevimab and cilgavimab is ongoing.

It is possible that variants resistant to tixagevimab and cilgavimab could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. The combination of tixagevimab and cilgavimab retained activity against pseudotyped VLPs harboring individual SARS-CoV-2 spike substitutions (K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, E484D/K/Q, F486V, F490S, Q493K/R, and S494P) identified in neutralization escape variants of other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with tixagevimab and cilgavimab.

13.2 Animal Toxicology and Pharmacology

In a toxicology study in cynomolgus monkeys, tixagevimab and cilgavimab had no adverse effects when administered via IM injection.

In tissue cross-reactivity studies with tixagevimab and cilgavimab using human adult and fetal tissues no binding of clinical concern was detected.

Tixagevimab and cilgavimab have been assessed in rhesus macaque and cynomolgus macaque models of SARS-CoV-2 infection. Prophylactic administration of tixagevimab and cilgavimab (N= 4 rhesus macaque; N= 3 cynomolgus macaque) three days prior to infection prevented SARS-CoV-2 infection of the upper and lower respiratory tracts in dose-dependent manner. Prophylactic administration of 4 mg/kg tixagevimab and cilgavimab resulted in a 7-$\log_{10}$ reduction in viral sub-genomic messenger RNA (sgmRNA) in nasopharyngeal swabs and 5 to 6-$\log_{10}$ reduction in sgmRNA or infectious virus titer in bronchoalveolar lavage samples at Day 2 post-challenge in all animals relative to placebo-treated animals. Compared to placebo, prophylactic administration of tixagevimab and cilgavimab (N= 3 cynomolgus macaque) reduced lung injury associated with SARS-CoV-2 infection.

The applicability of these findings to a clinical setting is not known.

14 CLINICAL STUDIES

The data supporting this EUA are based on analyses from the Phase III trials PROVENT (NCT04625725) and STORM CHASER (NCT04625972). Both trials are evaluating the safety and efficacy of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) for the prophylaxis SARS-CoV-2 symptomatic illness (COVID-19).

Efficacy Data from PROVENT

PROVENT is an ongoing Phase III, randomized (2:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the pre-exposure prophylaxis of COVID-19 in adults ≥18 years of age. All subjects were either ≥60 years of age, had a pre-specified co-morbidity (obesity, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, immunocompromised state, or previous history of severe or serious adverse event after receiving any approved vaccine), or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine. Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

The baseline demographics were balanced across the EVUSHELD and placebo arms. The median age was 57 years (with 43% of subjects aged 60 years or older), 46% of subjects were female, 73% were White, 3% were Asian 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5,197 subjects, 78% had baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19, including obesity (42%), diabetes (14%), cardiovascular disease (8%), cancer, including a history of cancer (7%), chronic obstructive pulmonary disease (5%), chronic kidney

disease (5%), chronic liver disease (5%), immunosuppressive medications (3%) and immunosuppressive disease (<1%).

For the primary endpoint, a subject was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred after administration and prior to Day 183. The primary analysis included 5,172 subjects who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3,441 received EVUSHELD and 1,731 received placebo. Only events that occurred prior to unblinding or vaccine receipt were included. EVUSHELD receipt resulted in a statistically significant (p-value <0.001) 77% reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) when compared to placebo (Table 7). At the time of analysis the median follow-up time post-administration was 83 days (range 3 to 166 days).

Similar results were observed for EVUSHELD recipients compared to placebo recipients in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause (12/3,441 versus 19/1,731, respectively) with relative risk reduction of 69% (95% CI: 36, 85; p-value= 0.002), and in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness regardless of unblinding or vaccine receipt (10/3,441 versus 22/1,731, respectively) with relative risk reduction of 77% (95% CI: 52, 89 ; p-value <0.001).

Table 7 Incidence of Symptomatic COVID-19 in Adults (PROVENT)

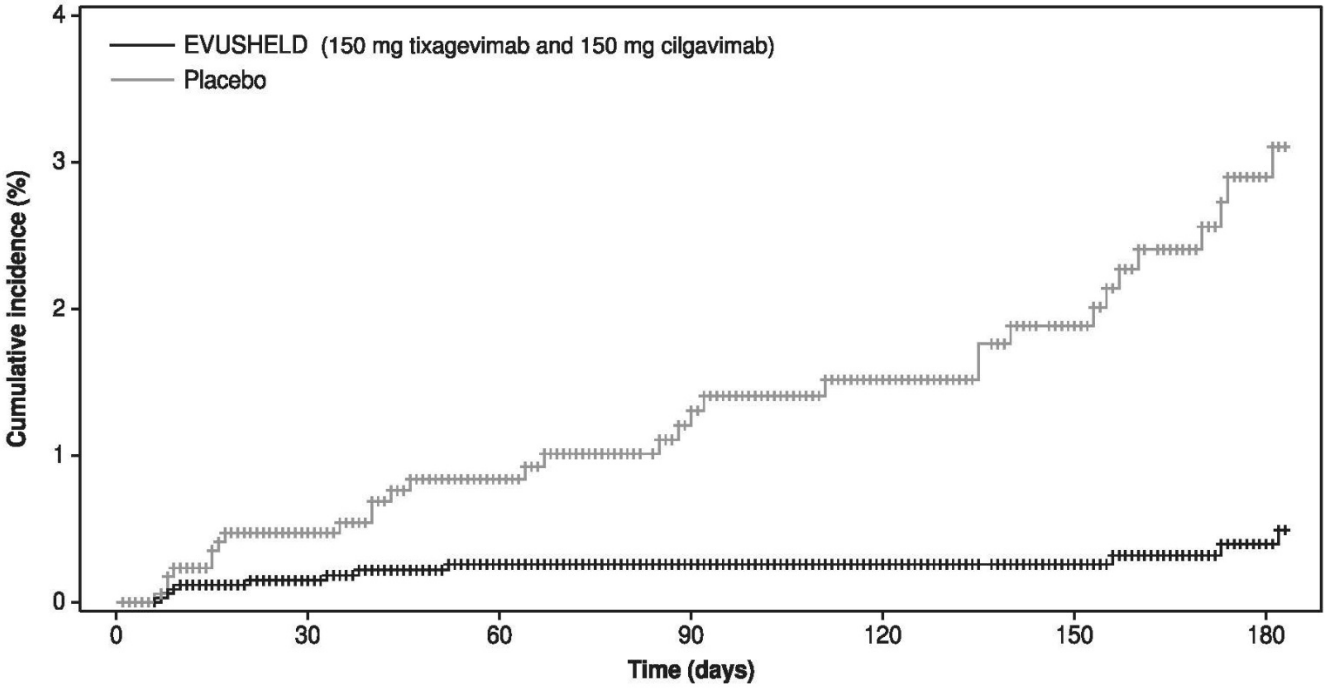
	N*	Number of events, n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD†	3,441	8 (0.2%)	77% (46, 90)
Placebo	1,731	17 (1.0%)	

N = number of subjects in analysis; CI = Confidence Interval
* subjects were censored after receiving the vaccine or being unblinded to consider the vaccine, whichever occurred earlier
† EVUSHELD dose (150 mg tixagevimab and 150 mg cilgavimab)

Among subjects who received EVUSHELD, there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR-positive symptomatic illness characterized by a minimum of either pneumonia [fever, cough, tachypnoea or dyspnea, and lung infiltrates] or hypoxemia [SpO_2 <90% in room air and/or severe respiratory distress] and a WHO Clinical Progression Scale score of 5 or higher) compared to one event (0.1%) among subjects who received placebo.

An additional data cut was conducted to provide post-hoc updated efficacy and safety analysis, the median follow-up was 6.5 months for subjects in both EVUSHELD and placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 83% (95% CI: 66, 91) with 11/3,441 (0.3%) events in the EVUSHELD arm and 31/1,731 (1.8%) events in the placebo arm, see Figure 1. These results are consistent with the duration of protection predicted by population PK modelling. Among subjects who received EVUSHELD there were no severe/critical COVID-19 events compared to five events among subjects who received placebo.

Figure 1 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (PROVENT)



Number of participants at risk

EVUSHELD	3441	2957	2393	2054	1815	1667	1044
Placebo	1731	1483	1177	991	856	774	472

* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183. Subjects who were unblinded/vaccinated prior to an event are also censored at the earlier time of unblinding/vaccination.

Efficacy Data from STORM CHASER

STORM CHASER is an ongoing Phase III randomized (2:1), double-blind, placebo-controlled clinical trial of EVUSHELD for the post-exposure prophylaxis of COVID-19 in adults ≥18 years of age. Subjects who had not previously received a COVID-19 vaccine were enrolled following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

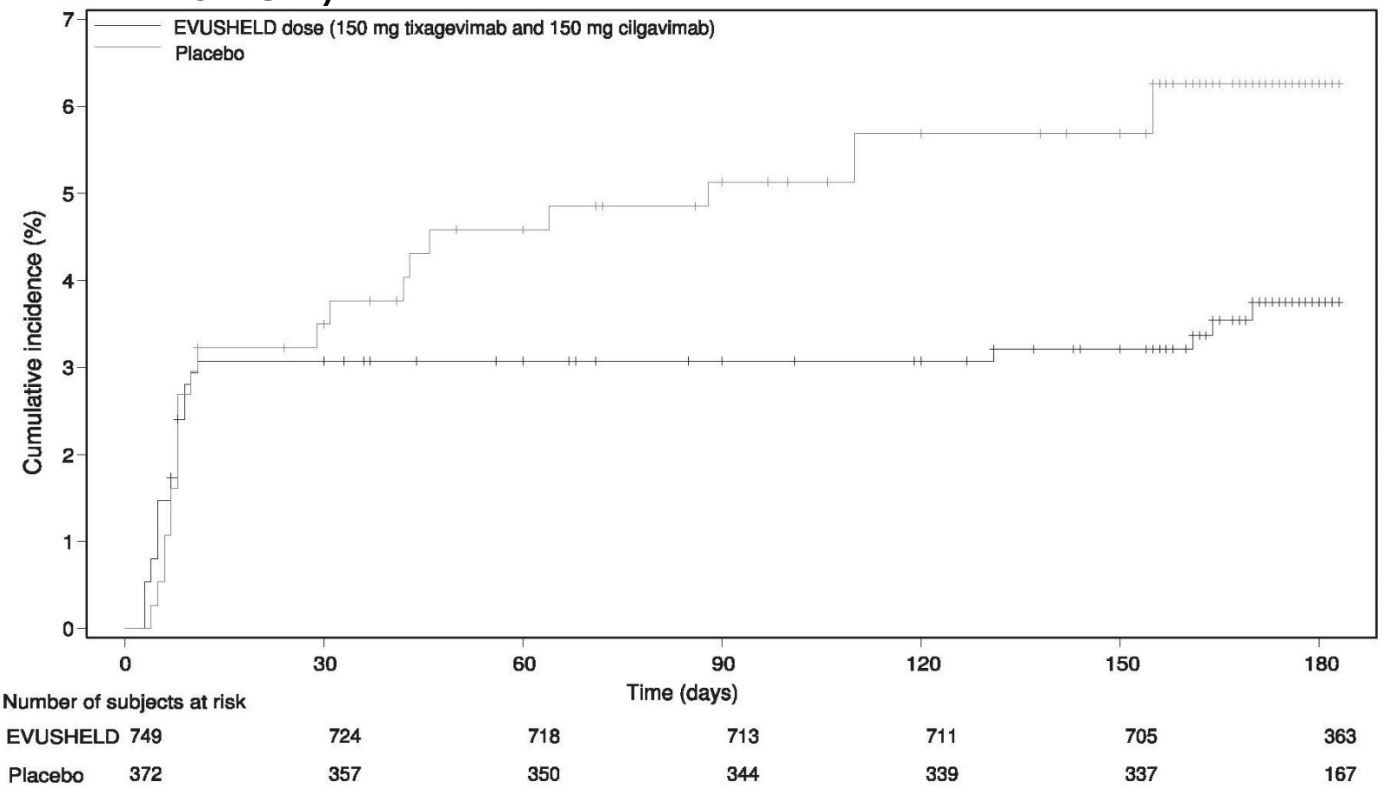
Of the 1,121 subjects who were randomized and received EVUSHELD (N= 749) or placebo (N= 372), 48 subjects were positive for SARS-CoV-2 (RT-PCR analysis of nasopharyngeal swabs) at baseline.

The primary efficacy analysis, comparison of the incidence of a subject's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post-dose and before Day 183, did not demonstrate a statistically significant effect for EVUSHELD versus placebo with 23 cases of symptomatic COVID-19 in the EVUSHELD arm (3.1%) and 17 cases in the placebo arm (4.6%) (relative risk reduction of 33%, 95% CI: -26, 65). At the time of analysis the median follow-up time post-administration was 49 days (range 5 to 115 days).

The study did not demonstrate benefit for EVUSHELD in preventing symptomatic COVID-19 in the first 30 days after randomization, leading to the limitation of use for post-exposure prophylaxis *[see Emergency Use Authorization (1)]*. However, there was a higher proportion of symptomatic COVID-19

cases among placebo recipients after Day 29 (see Figure 2 below, data from the post-hoc updated efficacy analysis with a median follow-up time of 6.5 months). EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

Figure 2 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (STORM CHASER)



* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Each EVUSHELD co-packaged carton contains two vials (Table 8):

- 1 single-dose vial of tixagevimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.
- 1 single-dose vial of cilgavimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.

Table 8 EVUSHELD co-packaged carton contents

Carton (2 vials per pack)	Components	
	1 vial of Tixagevimab 150 mg/1.5 mL (100 mg/mL) **(dark grey cap)**	**1 vial of Cilgavimab** 150 mg/1.5 mL (100 mg/mL) **(white cap)**
NDC 0310-7442-02	NDC 0310-8895-01	NDC 0310-1061-01

Storage and Handling

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Discard any unused portion.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient, parent and caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS OR CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of EVUSHELD.

Dosing
Advise patients that if they received the initial EVUSHELD dose of 150 mg tixagevimab and 150 mg of cilgavimab, they should received a second EVUSHELD dose of 150 mg of tixagevimab and 150 mg of cilgavimab as soon as possible *[see Dosage and Administration (2.1)]*.

Inform individuals that they may need to receive additional doses of EVUSHELD for ongoing protection but that the optimal timing of redosing is unknown at this time *[see Dosage and Administration (2), and Clinical Pharmacology (12.3)]*.

Cardiovascular Events
Inform individuals that a higher proportion of subjects who received EVUSHELD versus placebo reported cardiovascular serious adverse events (myocardial infarctions and heart failure). Advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event *[see Warnings and Precautions (5.3)]*.

For additional information, please visit the website or call the telephone number provided below.

To access the most recent EVUSHELD Fact Sheets, please scan the QR code provided below.

Website	Telephone number
http://www.evusheld.com 	1-800-236-9933

18 MANUFACTURER INFORMATION

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Manufactured by: Samsung Biologics, 300 Songdo bio-daero, Yeonsu-gu, Incheon 21987, Republic of Korea

Fact Sheet for Patients, Parents And Caregivers Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab) for Coronavirus Disease 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with EVUSHELD (tixagevimab co-packaged with cilgavimab) for pre-exposure prophylaxis for prevention of coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus.

This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking EVUSHELD, which you have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make EVUSHELD available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). EVUSHELD is not an FDA-approved medicine in the United States.

Read this Fact Sheet for information about EVUSHELD. Talk to your healthcare provider if you have any questions. It is your choice to receive or not receive EVUSHELD.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

What is EVUSHELD (tixagevimab co-packaged with cilgavimab)?
EVUSHELD is an investigational medicine used in adults and adolescents (12 years of age and older who weigh at least 88 pounds [40 kg]) for pre-exposure prophylaxis for prevention of COVID-19 in persons who are:

- not currently infected with SARS-CoV-2 and who have not had recent known close contact with someone who is infected with SARS-CoV-2 **and**
    - Who have moderate to severe immune compromise due to a medical condition or have received immunosuppressive medicines 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 (such as severe allergic reaction) to a COVID-19 vaccine(s) or COVID-19 vaccine ingredient(s).

EVUSHELD is investigational because it is still being studied. There is limited information known about the safety and effectiveness of using EVUSHELD for pre-exposure prophylaxis for prevention of COVID-19. EVUSHELD is not authorized for post-exposure prophylaxis for prevention of COVID-19.

The FDA has authorized the emergency use of EVUSHELD for pre-exposure prophylaxis for prevention of COVID-19 under an Emergency Use Authorization (EUA).

What should I tell my healthcare provider before I receive EVUSHELD?
Tell your healthcare provider if you:

- Have any allergies
- Have low numbers of blood platelets (which help blood clotting), a bleeding disorder, or are taking anticoagulants (to prevent blood clots)
- Have had a heart attack or stroke, have other heart problems, or are at high-risk of cardiac (heart) events
- Are pregnant or plan to become pregnant
- Are breastfeeding a child
- Have any serious illness
- Are taking any medications (prescription, over-the-counter, vitamins, or herbal products)

How will I receive EVUSHELD?

- EVUSHELD consists of two investigational medicines, tixagevimab and cilgavimab.
- You will receive 1 dose of EVUSHELD, consisting of 2 separate injections (tixagevimab and cilgavimab).
- EVUSHELD will be given to you by your healthcare provider as 2 intramuscular injections, given one after the other.

You may need to receive additional doses of EVUSHELD for ongoing protection. Viruses can change over time (mutate) and develop into a slightly different form of the virus, called a variant. The duration that EVUSHELD will protect you from infection may change with certain variants. The best timing for you to receive additional doses of EVUSHELD, if needed, is not known right now, because this depends on which SARS-CoV-2 variants will be present in the future.

Talk to your healthcare provider about receiving additional doses of EVUSHELD for ongoing protection and for further instructions. You can keep up-to-date with the latest information by visiting http://www.evusheld.com or by scanning the QR code, below:

Who should generally not take EVUSHELD?
Do not take EVUSHELD if you have had a severe allergic reaction to EVUSHELD or any ingredient in EVUSHELD.

What are the important possible side effects of EVUSHELD?
Possible side effects of EVUSHELD are:

- **Allergic reactions**. Allergic reactions can happen during and after injection of EVUSHELD. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low or high blood pressure, rapid or slow heart rate, chest discomfort or pain, weakness, confusion, feeling tired, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, dizziness and sweating. These reactions may be severe or life threatening.
- **Cardiac (heart) events**: Serious cardiac adverse events have happened, but were not common, in people who received EVUSHELD and also in people who did not receive EVUSHELD in the clinical trial studying pre-exposure prophylaxis for prevention of COVID-19. In people with risk factors for cardiac events (including a history of heart attack), more people who received EVUSHELD experienced serious cardiac events than people who did not receive EVUSHELD. It is not known if these events are related to EVUSHELD or underlying medical conditions. Contact your healthcare provider or get medical help right away if you get any symptoms of cardiac events, including pain, pressure, or discomfort in the chest, arms, neck, back, stomach or jaw, as well as shortness of breath, feeling tired or weak (fatigue), feeling sick (nausea), or swelling in your ankles or lower legs.

The side effects of getting any medicine by intramuscular injection may include pain, bruising of the skin, soreness, swelling, and possible bleeding or infection at the injection site.

These are not all the possible side effects of EVUSHELD. Not a lot of people have been given EVUSHELD. Serious and unexpected side effects may happen. EVUSHELD is still being studied so it is possible that all of the risks are not known at this time.

It is possible that EVUSHELD may reduce your body’s immune response to a COVID-19 vaccine. If you have received a COVID-19 vaccine, you should wait to receive EVUSHELD until at least 2 weeks after COVID-19 vaccination.

What other prevention choices are there?
Vaccines to prevent COVID-19 are approved or available under Emergency Use Authorization. Use of EVUSHELD does not replace vaccination against COVID-19. For more information about other medicines authorized for treatment

or prevention of COVID-19 go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for more information.

It is your choice to receive or not receive EVUSHELD. Should you decide not to receive EVUSHELD, it will not change your standard medical care.

EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19.

What if I am pregnant or breastfeeding?
If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with EVUSHELD?
Contact your healthcare provider if you have any side effects that bother you or do not go away. Report side effects to FDA MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088 or call AstraZeneca at 1-800-236-9933.

Additional Information
If you have questions, visit the website or call the telephone number provided below.

To access the most recent EVUSHELD Fact Sheets, please scan the QR code provided below.

Website	Telephone number
http://www.evusheld.com	1-800-236-9933

How can I learn more about COVID-19?

- Ask your healthcare provider.
- Visit https://www.cdc.gov/COVID19
- Contact your local or state public health department.

What is an Emergency Use Authorization?
The United States FDA has made EVUSHELD (tixagevimab co-packaged with cilgavimab) available under an emergency access mechanism called an Emergency Use Authorization EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

EVUSHELD for pre-exposure prophylaxis for prevention of coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the

total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for EVUSHELD is in effect for the duration of the COVID-19 declaration justifying emergency use of EVUSHELD, unless terminated or revoked (after which EVUSHELD may no longer be used under the EUA).

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Manufactured by: Samsung Biologics, 300 Songdo bio-daero, Yeonsu-gu, Incheon 21987, Republic of Korea

Subject: Updated Emergency Use Authorization (EUA) Dosage Recommendations for EVUSHELD (tixagevimab co-packaged with cilgavimab)

Dear Healthcare Provider:

The EVUSHELD (tixagevimab co-packaged with cilgavimab) dosage recommendations under the Emergency Use Authorization (EUA) have been revised based on decreased neutralization activity of EVUSHELD against the Omicron subvariants BA.1 and BA.1.1 (BA.1+R346K).

The revised authorized dosage regimen for EVUSHELD requires an increase in the initial dose. The revised authorized dosage regimen is as follows:

Initial Dosing:
The initial dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered as two separate consecutive intramuscular (IM) injections.

Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg of Cilgavimab:
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**. Any subsequent repeat dosing should be timed from the date of the second EVUSHELD dose. Refer to Table 2 below.

Repeat Dosing:
Because it is unclear which SARS-CoV-2 variant or Omicron subvariant will become dominant in the United States over the next few months, **the recommended timing for repeat dosing cannot be provided at this time**. The Fact Sheets will be revised with repeat dosing recommendations in the near future when more data are available to determine the appropriate timing of redosing. Providers should refer to the most recent Fact Sheet for repeat dosing recommendations.

HEALTHCARE PROVIDER ACTION

Healthcare providers should refer to the most current EUA Fact Sheet (www.evusheld.com) for the most accurate information as there are important differences concerning preparation and administration of the initial and repeat dosing of EVUSHELD.

To minimize dose preparation and administration errors, it is critical that **all orders for EVUSHELD** specify the numeric dose of each monoclonal antibody within EVUSHELD as follows:

- 300 mg of tixagevimab and 300 mg of cilgavimab, or
- 150 mg of tixagevimab and 150 mg of cilgavimab

Each carton of EVUSHELD contains two vials (one vial of 150 mg/1.5 mL tixagevimab and one vial of 150 mg/1.5 mL cilgavimab). There are **differences in product preparation** based on the prescribed dosage as outlined in Table 1 and 2 below:

Table 1. Initial Dosing of 300 mg of Tixagevimab and 300 mg of Cilgavimab

	Antibody dose	Number of vials needed	Volume to withdraw from vials
EVUSHELD* (tixagevimab co-packaged with cilgavimab)	tixagevimab 300 mg	2 vials	3 mL * **(1.5 ml from each vial into the same syringe)**
	cilgavimab 300 mg	2 vials	3 mL * **(1.5 ml from each vial into the same syringe)**

*Each carton of EVUSHELD contains one vial of tixagevimab 150 mg/1.5 mL and one vial of cilgavimab 150 mg/1.5 mL. The 300 mg of tixagevimab and 300 mg of cilgavimab doses are to be administered as separate, consecutive intramuscular injections. Withdraw the 3 mL of tixagevimab solution and 3 mL of cilgavimab solution into TWO separate syringes. Each vial has overfill to enable withdrawal of 1.5 ml from each vial. **Any leftover product should be discarded.**

Table 2. Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg of Cilgavimab 150 mg of Tixagevimab and 150 mg of Cilgavimab

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial(s)
	tixagevimab 150 mg	1 vial	1.5 mL*
	cilgavimab 150 mg	1 vial	1.5 mL*

* Each carton of EVUSHELD contains one vial of tixagevimab 150 mg/1.5 mL and one vial of cilgavimab 150 mg/1.5 mL. The 150 mg of tixagevimab and 150 mg of cilgavimab doses are to be administered as separate, consecutive intramuscular injections. Withdraw the 1.5 mL of tixagevimab solution and 1.5 mL of cilgavimab solution into TWO separate syringes. Each vial has overfill to enable withdrawal of 1.5 ml from each vial. **Any leftover product should be discarded.**

Administer the two components of EVUSHELD consecutively as intramuscular (IM) injections at different injection sites one after the other. The location of the intramuscular (IM) injections for the 300 mg of tixagevimab and 300 mg of cilgavimab dose should be limited to large muscles that can accommodate this volume (e.g., the gluteal muscles or anterolateral thigh muscles).

The Emergency Use Authorization Fact Sheet for Healthcare Providers is included with this notice, available at www.evusheld.com or available by scanning the QR Code below:

Reporting Adverse Events

The prescribing healthcare provider and/or your designee must report all SERIOUS ADVERSE EVENTS and all MEDICATION ERRORS potentially related to EVUSHELD within 7 calendar days from the healthcare provider's awareness of the event (1) by submitting FDA Form 3500 online, (2) by downloading FDA Form 3500 and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form.

In addition, please fax a copy of all FDA MedWatch forms to AstraZeneca at 1-866-742-7984.

Report adverse events by visiting https://contactazmedical.astrazeneca.com, or calling AstraZeneca at 1-800-236-9933.

Sincerely,

XXXXXXX

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/

ANDREW A GENTLES
02/24/2022 11:28:35 AM

STEPHANIE B TROY
02/24/2022 11:31:16 AM

SARAH M CONNELLY
02/24/2022 11:33:31 AM

DEBRA B BIRNKRANT
02/24/2022 11:58:15 AM

ADAM I SHERWAT
02/24/2022 12:10:07 PM

Clinical Review

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRALS

DATE: February 24, 2022

SUBJECT: Addendum to 2.24.22 EUA 104 Summary Review Memo

In the final Letter of Authorization for the EUA 104 revision that took place on February 24, 2022, the condition of authorization was modified to specify that AstraZeneca must provide the Agency with a **final** protocol for this trial no later than **March 11, 2022**. The final condition of authorization is shown below:

- AstraZeneca will conduct an additional randomized, dose-ranging clinical trial in individuals with moderate to severe immunocompromise who may not mount an adequate immune response to COVID-19 vaccination evaluating the following dosing regimens for COVID-19 pre-exposure prophylaxis:
    - EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) administered as two consecutive IM injections followed 3 months later by EVUSHELD (150 mg tixagevimab and 150 mg cilgavimab) administered as two consecutive IM injections with subsequent redosing every 3 months.
    - EVUSHELD (600 mg tixagevimab and 600 mg cilgavimab) administered as an intravenous infusion followed 6 months later by EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) administered as two consecutive IM injections with subsequent redosing every 6 months

  At least 100 subjects should be randomized to each dosing regimen. The primary objectives of the trial would be to evaluate safety and immunogenicity, but pharmacokinetic, pharmacodynamic, and efficacy data should also be collected. AstraZeneca must provide the Agency with a final protocol for this trial no later than March 11, 2022.

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/

STEPHANIE B TROY
02/24/2022 03:34:44 PM

SARAH M CONNELLY
02/24/2022 03:36:48 PM

DEBRA B BIRNKRANT
02/24/2022 03:40:14 PM

ADAM I SHERWAT
02/24/2022 03:42:51 PM