

EVUSHELD USER GUIDE

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.

IMPORTANT SAFETY INFORMATION

EVUSHELD™ (tixagevimab co-packaged with cilgavimab) has not been approved, but has been granted an Emergency Use Authorization (EUA) by FDA. There are limited clinical data available and serious and unexpected adverse events may occur that have not been previously reported with EVUSHELD use.

Contraindication:

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

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

 **EVUSHELD™**
(tixagevimab co-packaged with cilgavimab)

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ABOUT THIS GUIDE

- This guide is for healthcare professionals
- It covers information about EVUSHELD that is most important to you, including identifying patients, dosing and administration, and clinical data
- This guide should be used in conjunction with the [Fact Sheet for Healthcare Providers](#)

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 the U.S. Department of Health and Human Services 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 an FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (ie, 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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Warnings and Precautions:

Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with IgG1 monoclonal antibodies like 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.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

EVUSHELD — 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), a 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 (eg, 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.

*For additional information, please see [CDC Clinical Considerations](#). 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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Warnings and Precautions: (Cont'd)

Clinically Significant Bleeding Disorders

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

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

MEDICAL CONDITIONS

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

- Active treatment for solid tumor and hematologic malignancies
- 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 (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts $<200/\text{mm}^3$, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (ie, ≥ 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 factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (eg, B-cell depleting agents)

*For additional information, please see [CDC Clinical Considerations](#). Healthcare providers should consider the benefit-risk for an individual patient.

INFORMATION REGARDING AVAILABLE ALTERNATIVES

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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Warnings and Precautions: (Cont'd)

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 at baseline. 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.

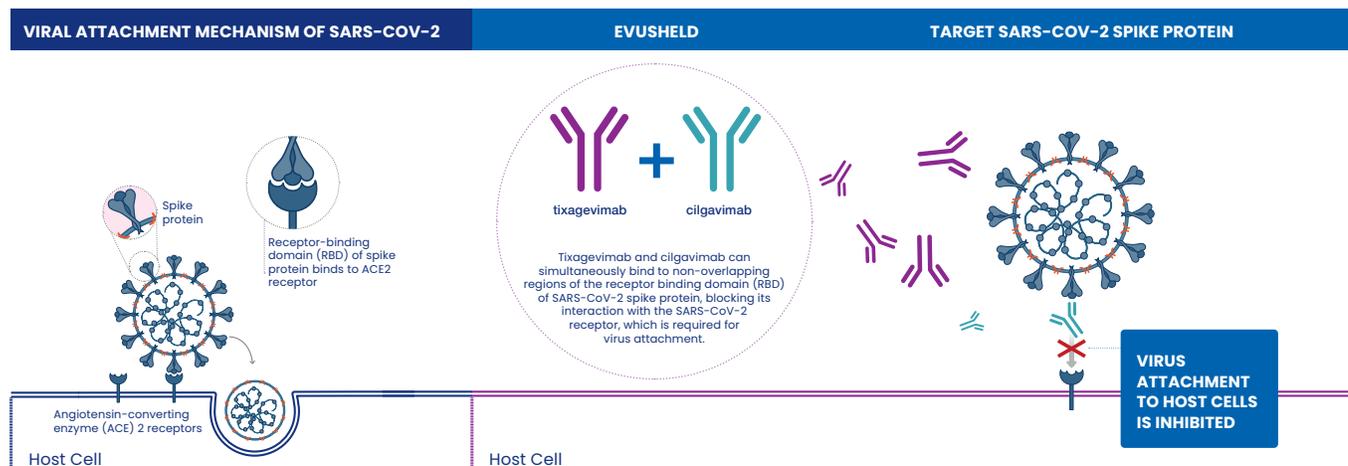
Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

MECHANISM OF ACTION

Tixagevimab and cilgavimab are two recombinant human IgG1 κ 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.

EVUSHELD: COMBINATION OF 2 MONOCLONAL ANTIBODIES WHICH ARE SARS-COV-2 SPIKE PROTEIN-DIRECTED ATTACHMENT INHIBITORS



Serious hypersensitivity reactions, including anaphylaxis, have been observed with human immunoglobulin G1 (IgG1) monoclonal antibodies like EVUSHELD. 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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Adverse Reactions:

The most common adverse events are headache, fatigue and cough.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

DOSING & ADMINISTRATION

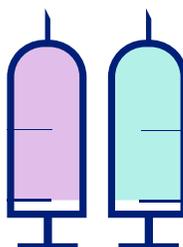
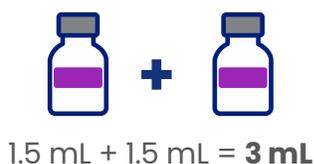


Each EVUSHELD carton contains two vials; one of each antibody. Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

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.

**2 VIALS: tixagevimab solution
(150 mg/1.5 mL)**



**2 VIALS: cilgavimab solution
(150 mg/1.5 mL)**

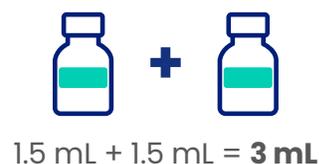


Table 1. Dosage of 300 mg of Tixagevimab and 300 mg of Cilgavimab

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.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, and in individuals with renal impairment.

Please see [Fact Sheet for Healthcare Providers](#) for complete dosing and administration instructions.

IMPORTANT SAFETY INFORMATION (Cont'd)

Use in Specific Populations:

Pregnancy

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.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

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

Individuals who have already received the previously authorized initial dose (150 mg of tixagevimab and 150 mg of cilgavimab) **should receive an additional EVUSHELD dose as soon as possible.**

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

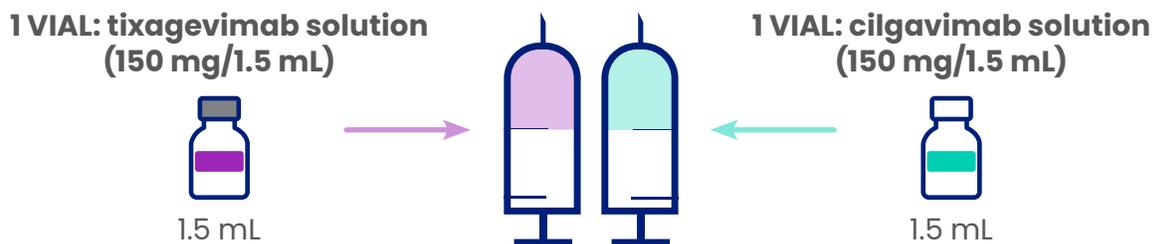


Table 2. Dosage of 150 mg of Tixagevimab and 150 mg of Cilgavimab

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.

Tixagevimab and cilgavimab are each supplied in individual single-dose vials. Do not shake the vials.

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

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

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

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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Use in Specific Populations: (Cont'd)

Lactation

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.

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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 and Caregivers](#) and provide them with a copy of the Fact Sheet prior to administration of EVUSHELD.

STEP-BY-STEP PROCESS



EVUSHELD must be prepared by a qualified healthcare provider.

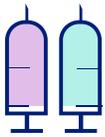
1



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**.

2



Withdraw the appropriate amount of tixagevimab solution and the appropriate amount of cilgavimab solution into **TWO separate syringes**. **Discard unused portion in vials**.

3



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).

4



Clinically monitor individuals after injections and observe for at least 1 hour.

5

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.

IMPORTANT SAFETY INFORMATION (Cont'd)

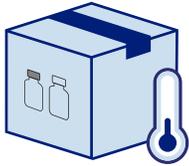
Use in Specific Populations: (Cont'd)

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.

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STORAGE



- Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light
- Do not freeze. Do not shake
- 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 2°C to 8°C (36°F to 46°F), or
 - at room temperature up to 25°C (77°F)

IMPORTANT SAFETY INFORMATION (Cont'd)

SARS-CoV-2 Viral Variant

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

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EVUSHELD 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 of SARS-CoV-2 symptomatic illness (COVID-19).

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.

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.

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Contraindication:

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

Warnings and Precautions:

Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with IgG1 monoclonal antibodies like 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.

Clinically Significant Bleeding Disorders

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

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PROVENT BASELINE DEMOGRAPHICS

Baseline demographics were balanced across EVUSHELD and placebo arms.

CHARACTERISTIC	
Median age	57 years
Female	46%
White	73%
Asian	3%
Black/African American	17%
Hispanic/Latino	15%
Baseline co-morbidities	78%

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%).

IMPORTANT SAFETY INFORMATION (Cont'd)

Warnings and Precautions: (Cont'd)

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 at baseline. 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.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

PROVENT EFFICACY DATA

PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg of cilgavimab])

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. 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).

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)

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. These results are consistent with the duration of protection predicted by population PK modeling.

IMPORTANT SAFETY INFORMATION (Cont'd)

Adverse Reactions:

The most common adverse events are headache, fatigue and cough.

Use in Specific Populations:

Pregnancy

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.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

STORM CHASER EFFICACY DATA

STORM CHASER (EVUSHELD [150 mg of tixagevimab and 150 mg of cilgavimab])

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. However, there was a higher proportion of symptomatic COVID-19 cases among placebo recipients after Day 29. EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

IMPORTANT SAFETY INFORMATION (Cont'd)

Use in Specific Populations: (Cont'd)

Lactation

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.

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.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

ADVERSE REACTIONS FROM CLINICAL STUDIES

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. 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 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.

PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg of cilgavimab])

In the Phase III PROVENT trial, adverse events were reported in 1,221 (35%) subjects receiving EVUSHELD and 593 (34%) receiving placebo. Serious adverse events (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 the table below.

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 the table below.

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%

IMPORTANT SAFETY INFORMATION (Cont'd)

SARS-CoV-2 Viral Variant

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

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

ADVERSE REACTIONS FROM CLINICAL STUDIES (Cont'd)

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. 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.

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.

IMPORTANT SAFETY INFORMATION

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Contraindication:

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

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

ADVERSE REACTIONS FROM CLINICAL STUDIES (Cont'd)

STORM CHASER (EVUSHELD [150 mg of tixagevimab and 150 mg of cilgavimab])

Adverse events were reported in 162 (22%) subjects receiving EVUSHELD and 111 (30%) receiving placebo. Serious adverse events 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.

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).

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.

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).

In TACKLE, 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 $\geq 1\%$) among subjects receiving EVUSHELD compared to those receiving placebo.

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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Warnings and Precautions:

Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with IgG1 monoclonal antibodies like 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.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

USE OF EVUSHELD IN SPECIFIC POPULATIONS

Pregnancy

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.

Lactation

There are no available data on the presence of tixagevimab and 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.

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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Warnings and Precautions: (Cont'd)

Clinically Significant Bleeding Disorders

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

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 at baseline. 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.

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USE OF EVUSHELD IN SPECIFIC POPULATIONS (Cont'd)

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.

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.

Hepatic Impairment

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

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.

IMPORTANT SAFETY INFORMATION (Cont'd)

Adverse Reactions:

The most common adverse events are headache, fatigue and cough.

Please see additional [Important Safety Information](#) throughout and see [Fact Sheet for Healthcare Providers](#) for information on the authorized use of EVUSHELD and mandatory requirements of the EUA.

ADDITIONAL RESOURCES

[American Academy of Family Physicians](#)

Daily COVID-19 research briefings

[Association of State and Territorial Health Officials](#)

Podcasts, webinars, videos, and other resources

[AstraZeneca COVID-19 Hub](#)

An overview of AstraZeneca news and relevant information

[Black Doctors COVID-19 Consortium](#)

COVID-19 resources, education, and advocacy for African Americans

[Centers for Disease Control and Prevention](#)

Information about COVID-19 for healthcare workers

[COVID-19 Therapeutics](#)

COVID-19 therapeutics announcements and more

[US Department of Health and Human Services](#)

Includes current information about COVID-19 treatments

[COVID-19 Real-Time Learning Network](#)

Resources include links to latest news, podcasts, events, and ways to connect to clinicians

[US Food and Drug Association COVID-19 Information](#)

Latest information about COVID-19 from the FDA

[World Health Organization COVID-19 Information](#)

COVID-19 information portal of WHO

FOR MORE INFORMATION ABOUT EVUSHELD, PLEASE VISIT
[EVUSHELD.com](https://www.evusheld.com) or scan the QR code.



IMPORTANT SAFETY INFORMATION

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Contraindication:

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

Warnings and Precautions:

Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with IgG1 monoclonal antibodies like 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.

Clinically Significant Bleeding Disorders

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

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 at baseline. 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.

Adverse Reactions:

The most common adverse events are headache, fatigue and cough.

Use in Specific Populations:

Pregnancy

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.

Lactation

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.

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.

AUTHORIZED USE

EVUSHELD™ (tixagevimab co-packaged with cilgavimab) is authorized for use under an EUA for the 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).

IMPORTANT SAFETY INFORMATION (Cont'd)

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.

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

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.

[The FDA Letter of Authorization](#) is available for reference, as well as the [Fact Sheet for Patients, Parents And Caregivers](#).

SARS-CoV-2 Viral Variant

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

Reporting Adverse Events

The prescribing healthcare provider and/or your designee must report all SERIOUS ADVERSE EVENTS and 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.