NEW DRUG APPROVAL

Brand Name	Evusheld™
Generic Name	tixagevimab co-packaged with cilgavimab
Drug Manufacturer	AstraZeneca Pharmaceuticals LP

New Drug Approval

FDA Approval Date: December 8, 2021
Review Designation: Orphan
Type of Review: Emergency Use Authorization (EUA)
Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Coronaviruses are the largest, enveloped, single-stranded positive-sense RNA viruses, including 4 generation: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Alpha- and Betacoronaviruses mainly infect mammals; the rest of two primarily infect birds. Seven coronaviruses that related to human disease had been identified. Four human coronaviruses (HCoV 229E, NL63, OC43, and HKU1) had been endemic globally and just resulted in upper respiratory tract infections in adults. Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus (SARS-CoV-2). Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow).

In December 2019, pneumonia of unknown cause occurred in Wuhan (China). On January 7, 2020, a novel corona virus, named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was identified in the throat swab sample of 1 patient. Globally, over 55 million confirmed cases of COVID-19 have been reported in all continents except Antarctica.

Efficacy

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 SARSCoV-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-CoV2 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 6). 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).

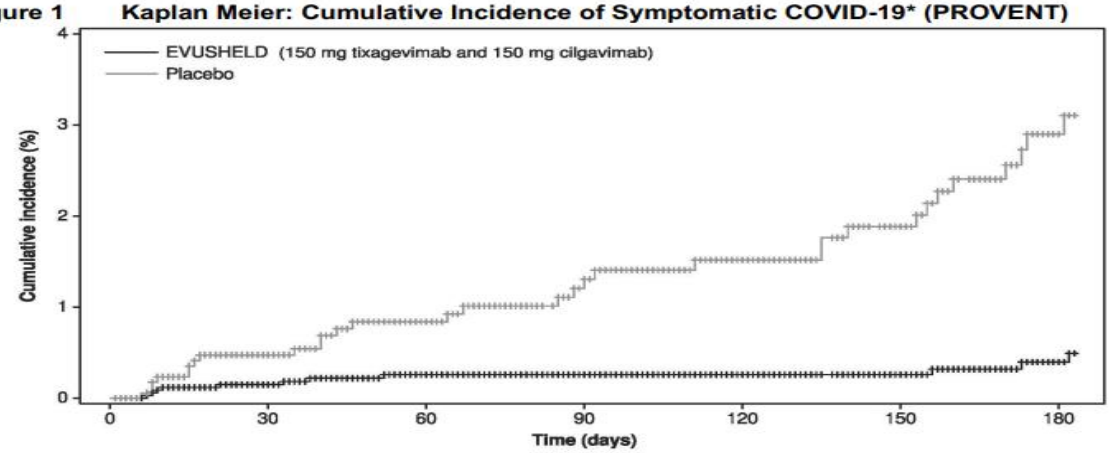
Table- Incidence of Symptomatic COVID-19 in Adults (PROVENT)

	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 [SpO2 <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 (below 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:

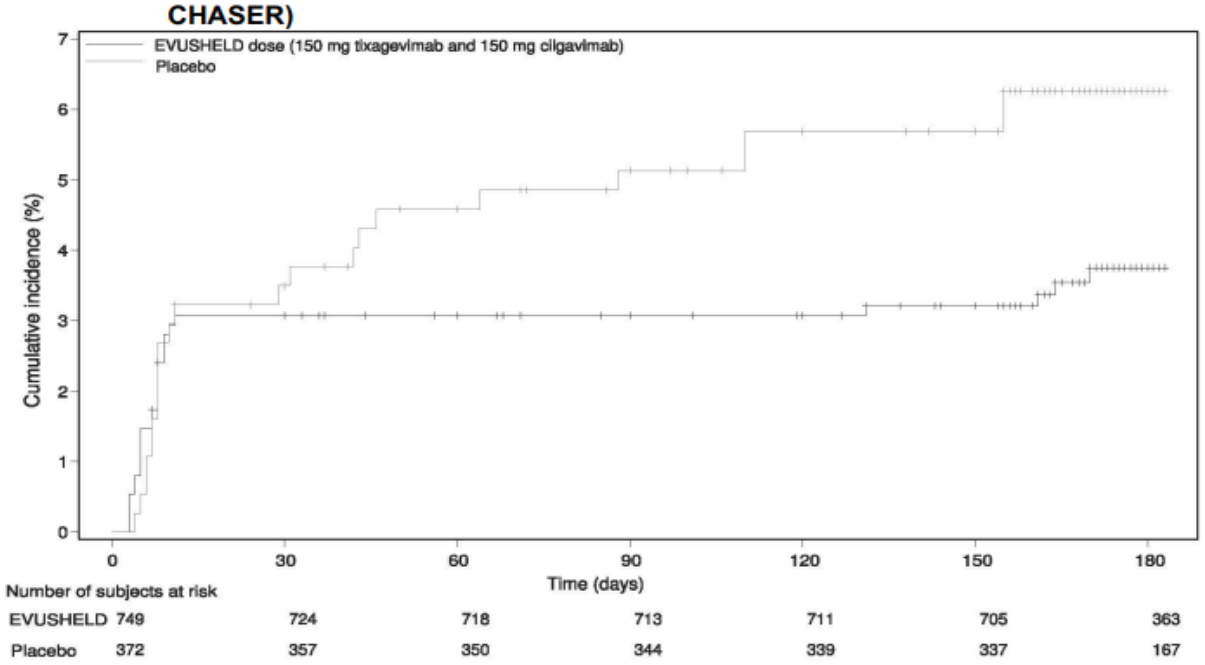
STORM CHASER is an ongoing Phase III randomized (2:1), double-blind, placebo-controlled clinical trial of Evusheld™ for the post-exposure prophylaxis of COVID-19 in adults ≥18 years of age. Subjects who had not previously received a COVID-19 vaccine were enrolled following potential exposure (within 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. 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 postexposure 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.

Safety

ADVERSE EVENTS

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

WARNINGS & PRECAUTIONS

Hypersensitivity Including Anaphylaxis
Serious hypersensitivity reactions, including anaphylaxis, have been observed with Human immunoglobulin G1 (IgG1) monoclonal antibodies like Evusheld™.
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
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.

CONTRAINDICATIONS

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

Clinical Pharmacology

MECHANISMS OF ACTION

Tixagevimab and cilgavimab are two recombinant human IgG1k 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 KD = 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 IC50 values of 0.32 nM (48 ng/mL), 0.53 nM (80 ng/mL), and 0.43 nM (65 ng/mL), respectively.

Dose & Administration

ADULTS

Weighing 40 kg or more: 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular (IM) injections.

PEDIATRICS

12 years and older weighing 40 kg or more: Refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment required.

HEPATIC IMPAIRMENT

No dosage adjustment required.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection:

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