▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

EVUSHELD™
tixagevimab and cilgavimab

1 NAME OF THE MEDICINE

Tixagevimab and cilgavimab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each carton of EVUSHELD contains two vials:

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

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear to opalescent, colourless to slightly yellow, pH 6.0 solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EVUSHELD (tixagevimab and cilgavimab) has **provisional approval** for the **pre-exposure prophylaxis** of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg,

- Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments that make it likely that they will not mount an adequate immune response to COVID-19 vaccination **or**
- For whom vaccination with any approved COVID-19 vaccine 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).

See Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties.

EVUSHELD is not recommended as a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

This decision has been made on the basis of short-term efficacy and safety data. Continued approval depends on the evidence of longer-term efficacy and safety data from ongoing clinical trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

Posology

The recommended dosage is 300 mg of EVUSHELD administered as two separate 1.5 mL, sequential injections of:

- 150 mg of tixagevimab
- 150 mg of cilgavimab

In clinical trials, EVUSHELD was not administered to subjects who have already received a COVID-19 vaccine (See Section 5.1 Clinical trials). The potential effect of EVUSHELD on the body's immune response to a COVID-19 vaccine is unknown.

Special patient populations

Paediatric use

The recommended dosing regimens are 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 clinical trial PROVENT (see Section 5.1 Pharmacodynamic properties and Section 5.2 Pharmacokinetic properties).

The safety and efficacy of EVUSHELD in children aged <18 years have not been established. No data are available.

Method of administration

Intramuscular (IM) injection.

Tixagevimab and cilgavimab should be administered as separate sequential IM injections at different injection sites, one in each of the gluteal muscles.

EVUSHELD has only been studied in single-dose studies. There are no safety and efficacy data available with repeat dosing.

Each carton of EVUSHELD contains two vials:

- tixagevimab solution for injection (dark grey vial cap);
- cilgavimab solution for injection (white vial cap).

Table 1 Dosage of tixagevimab and cilgavimab

Indication	**EVUSHELD dose** (tixagevimab and cilgavimab)	**Antibody dose**	**Number of vials needed**†	**Volume to withdraw from vial(s)**
Pre-exposure prophylaxis of COVID-19	300 mg (1 carton)	tixagevimab 150 mg	1 vial	1.5 mL
		cilgavimab 150 mg	1 vial	1.5 mL

† Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

Visually inspect the vials for particulate matter and discolouration. Both tixagevimab and cilgavimab are clear to opalescent, colourless to slightly yellow solutions. Discard the vials if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vials.

The solutions for injection do not contain a preservative 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 should not exceed 4 hours, either :

- in a refrigerator at 2ºC to 8ºC
- or at room temperature up to 25ºC.

The vials are for single use in one patient only. Any unused solution should be discarded.

4.3 CONTRAINDICATIONS

Individuals with a history of severe hypersensitivity reactions, including anaphylaxis, to the active substances or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed rarely with other IgG1 monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.

Clinically significant bleeding disorders

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

Cardiovascular and thromboembolic events

In PROVENT, there was a higher rate of cardiac serious adverse events (SAEs), including myocardial infarction (one fatal SAE) and cardiac failure, in subjects who received EVUSHELD compared to placebo. See Section 4.8 Adverse effects (Undesirable effects). All subjects who experienced cardiac SAEs had cardiovascular risk factors and/or a prior history of cardiovascular disease.

In PROVENT, there was a higher rate of thromboembolic serious adverse events (SAEs) in subjects who received EVUSHELD, compared to placebo. See Section 4.8 Adverse effects (Undesirable effects). One event of mesenteric artery thrombosis was reported as a SAE, 6 days after injection in a subject without a known medical history of coagulation disorders. A CT scan of the abdomen and pelvis at the time of the event showed atheromatous overload of vascular vessels. A possible relationship with EVUSHELD cannot be ruled out.

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.

Use in the elderly

See Section 5.2 Pharmacokinetic properties.

Paediatric use

The safety and efficacy of EVUSHELD in children aged <18 years has not been established. No data are available. See Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been conducted.

EVUSHELD is not expected to undergo metabolism by hepatic enzymes or renal elimination (see Section 5.2 Pharmacokinetic properties).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of tixagevimab and cilgavimab on human fertility.

Use in pregnancy – Category B2

There are limited data from the use of tixagevimab and cilgavimab in pregnant women.

Non-clinical reproductive toxicity studies have not been performed with tixagevimab and cilgavimab. In a tissue cross reactivity study with tixagevimab and cilgavimab using human fetal tissues no binding was detected.

EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the foetus.

Use in lactation

It is not known whether tixagevimab and cilgavimab are excreted in human milk. Exposure to the breast-fed child cannot be excluded.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for EVUSHELD and any potential adverse effects on the breast-fed child from EVUSHELD or from underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

EVUSHELD has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the Safety Profile

A total of 4210 adult participants have been exposed to 300 mg EVUSHELD, via IM injection for all phase III studies conducted in the prophylaxis setting.

The most frequently reported adverse reaction was injection site reaction (1.3%).

Adverse Reactions

Adverse Reactions (Table 2) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 2 Adverse reactions

MedDRA SOC	Preferred Term	Frequency†
Immune system disorders	Hypersensitivity*	Common
General disorders and administration site conditions	Injection related reaction	Uncommon
Injury, poisoning and procedural complications	Injection site reaction*	Common

* Grouped terms: Hypersensitivity (including Rash and Urticaria); Injection site reaction (including Injection site pain, Injection site erythema, Injection site pruritus, Injection site reaction and Injection site induration).
† Frequencies are based on exposure to 300 mg EVUSHELD in the pooled data from the prophylaxis studies.

PROVENT

PROVENT enrolled adults ≥18 years of age who were either ≥60 years of age, had pre-specified comorbidities, 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). The primary safety analysis was based on data through to an event driven efficacy data cut-off with a median (range) follow-up of 83 days (3-166 days). 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), the median and range of follow-up times were similar between EVUSHELD and placebo recipients.

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.

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

Adverse Reaction	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 that was reported at the time of the primary analysis.

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.

Table 4 Exposure Adjusted Incidence (EAIR) of Cardiac SAEs in PROVENT with Onset Prior to Day 183 Using the Median 6.5 Month Data Cut-off Date

System Organ Class Preferred term	**EVUSHELD 300 mg IM N = 3,461 Events (EAIR)**	**Placebo N = 1,736 Events (EAIR)**
Cardiac disorders*	23 (1.2)	5 (0.5)
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Acute left ventricular failure	0	1 (0.1)
Paroxysmal atrioventricular block	1 (0.1)	0
Cardiac failure congestive	4 (0.2)	0
Atrial fibrillation	1 (0.1)	2 (0.2)
Angina pectoris	1 (0.1)	0
Arrhythmia	1 (0.1)	0
Arteriosclerosis coronary artery	1 (0.1)	0
Cardiac failure	1 (0.1)	0
Cardiac failure acute	1 (0.1)	0
Cardio-respiratory arrest	1 (0.1)	0
Cardiomegaly	1 (0.1)	0
Cardiomyopathy	1 (0.1)	0
Coronary artery disease	1 (0.1)	0

*One EVUSHELD recipient and one placebo recipient had two cardiac SAEs each

Thromboembolic Serious Adverse Events

Through the additional data-cut-off in PROVENT, a higher incidence of thromboembolic SAEs was reported in subjects who received EVUSHELD, compared to placebo. A summary of thromboembolic SAEs are provided in Table 5.

Table 5 Exposure Adjusted Incidence Rate (EAIR) of thromboembolic events SAEs in PROVENT with Onset Prior to Day 183 Using the Median 6.5 Month Data Cut-off Date

System Organ Class Preferred term	**EVUSHELD 300 mg IM** **N = 3,461** **Events (EAIR)**	**Placebo** **N = 1,736** **Events (EAIR)**
Thromboembolic SAEs	**17 (0.9)**	**4 (0.4)**
Cardiac disorders		
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Gastrointestinal disorders		
Mesenteric artery thrombosis	1 (0.1)	0
Nervous system disorders		
Cerebral infarction	1 (0.1)	0
Transient ischaemic attack	2 (0.1)	0
Lacunar infarction	0	1 (0.1)
Cerebrovascular accident	2 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	2 (0.1)	0

Paediatric population

No data are available for paediatric patients <18 years old (See Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific treatment for overdose with EVUSHELD.

In clinical trials, doses up to 600 mg IM (300 mg each of tixagevimab and cilgavimab) and 3000 mg intravenously (1500 mg each of tixagevimab and cilgavimab) have been administered without dose-limiting toxicity.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies, with amino acid substitutions to extend antibody half-life (YTE) and to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Tixagevimab, cilgavimab and their combination bind to spike with equilibrium dissociation constants of K_D = 2.8 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with the human ACE2 receptor, resulting in a blockade of virus entry and effectively neutralising the SARS-CoV-2 virus. Tixagevimab, cilgavimab and their combination blocked RBD binding to the human ACE2 receptor 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.

Antiviral activity

In a SARS-CoV-2 virus neutralisation assay on Vero E6 cells, tixagevimab, cilgavimab and their combination neutralised 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. These *in vitro* values correlate with *in vivo* clinical effective serum concentrations of 2.2 µg/mL of EVUSHELD.

Antibody-dependent cell-mediated cytotoxicity (ADCC) was assessed using target cells that carry SARS-CoV-2 spike protein, with monoclonal antibody concentrations at a range of 25 µg/mL to 1.5 ng/mL. Antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent complement deposition (ADCD) were assessed using spike antigen-functionalised beads. ADCP activity was assessed with primary human neutrophils or THP-1 human monocytic cell line, with antibody concentrations at a range of 5 µg/mL to 2 ng/mL and 67 µg/mL to 30.6 ng/mL, respectively. ADCD activity was assessed with antibody concentrations at a range of 100 µg/mL to 46 ng/mL. Antibody-dependent NK cell activation (ADNKA) was assessed using primary human NK cells on spike-coated plates with monoclonal antibody concentrations at a range of 20 µg/mL to 9 ng/mL. Tixagevimab, cilgavimab and the tixagevimab and cilgavimab combination mediated no ADCP activity in primary human neutrophils and only limited ADCP activity in THP-1 cells. Tixagevimab, cilgavimab and the tixagevimab and cilgavimab combination did not mediate ADCC or ADNKA activity with human NK cells. Tixagevimab, cilgavimab and the tixagevimab and cilgavimab combination did not mediate ADCD activity with guinea pig complement proteins.

Antiviral 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 viral 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 pseudovirus into these cells.

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 TCID50 measurements, and lung injury and pathology based on histology measurements). No evidence of enhancement of 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.

Escape variants were identified following serial passage in cell culture of SARS-CoV-2 or recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein (pseudovirus) in the presence of cilgavimab or tixagevimab individually, or tixagevimab and cilgavimab in combination. Variants which showed reduced susceptibility to cilgavimab alone included spike protein amino acid substitutions R346I (>200-fold), K444E (>200-fold), and K444R (>200-fold). All variants maintained susceptibility to tixagevimab alone, and tixagevimab and cilgavimab in combination.

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

Most amino acid residues in the tixagevimab binding site (14 of 17 positions) and cilgavimab binding site (16 of 19 positions) have been >99% conserved among global isolates (N=2,620,237 whole genome sequences through 02 September 2021).

In neutralisation assays using recombinant SARS-CoV-2 pseudoviruses harbouring individual spike substitutions identified in circulating SARS-CoV-2, 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) and 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). Variants harbouring E484K (2.4- to 5.4-fold), Q493R (3.4-fold), E990A (5.7-fold), or T1009I (4.5-fold) exhibited low level reduced susceptibility to tixagevimab and cilgavimab in combination.

Tixagevimab and cilgavimab in combination retained full to nearly full neutralisation activity against pseudovirus and/or live virus SARS-CoV-2 variant strains harbouring all spike substitutions identified in Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Delta [+K417N] (AY.1/AY.2) variants of concern, and Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37) and Mu (B.1.621) variants of interest. Tixagevimab and cilgavimab in combination retained full to nearly full neutralisation activity against Epsilon (B.1.427 / B.1.429), R.1, B.1.1.519, C.36.2, B.1.214.2, and B.1.619.1 variant alerts for further monitoring and P.2, B.1.616, A.23.1, A.27, and AV.1 variants de-escalated from further monitoring.

Tixagevimab and cilgavimab in combination showed reduced neutralisation activity against pseudotyped VLPs expressing spike protein and authentic SARS-CoV-2 Omicron variant

(B.1.1.529), 132- to 183-fold [IC_{50} = 171 – 277 ng/mL] and 12- to 30-fold [IC50 = 147 – 273 ng/mL], respectively.

Pseudovirus SARS-CoV-2 spike variant strains with moderate reduced susceptibility to tixagevimab alone included those harbouring E484K (Alpha, 18.5-fold; Beta, 3.5- to 15-fold) and variants with moderate reduced susceptibility to cilgavimab alone included those with R346K:E484K:N501Y (Mu, 21-fold), as indicated above. Similar results were observed, where data was available, in neutralisation assays using authentic SARS-CoV-2 variants strains.

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

Table 6 Pseudovirus and Authentic SARS-CoV-2 Neutralisation Data for SARS-CoV-2 Variant Substitutions with Tixagevimab and Cilgavimab Together

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions Tested	Fold Reduction in Susceptibility[a]		IC_{50} (ng/mL)	
Pango Lineage (origin)	WHO Label		Pseudovirus[b]	Authentic SARS-CoV-2[c]	Pseudovirus [b]	Authentic SARS-CoV-2 [c]
B.1.1.7 (UK)	Alpha	N501Y	0.5- to 5.2 fold	No Change[d]	1.1-6.0	8.4-39.5
B.1.351 (South Africa)	Beta	K417N:E484K:N501Y	2.5 – 5.5[d]	No Change[d]	5.6-5.9	6.5-226
P.1 (Brazil)	Gamma	K417T:E484K:N501Y	No Change[d]	No Change[d]	2.7	3.2
B.1.617.2 (India)	Delta	L452R:T478K	No Change[d]	No Change[d]	2.2	7.5
AY.1/AY.2 (India)	Delta [+K417N]	K417N:L452R:T478K	No Change[d]	No Change[d]	1.9	ND
B.1.1.529 (South Africa)	Omicron	All identified[e]	132- to 183-fold	12- to 30-fold	171-277	147–273
B.1.525 (Multiple country)	Eta	E484K	No Change[d]	ND	9.5	ND
B.1.526 (United States)	Iota	E484K	No Change[d]	No Change[d]	4.5	1.0-7.0
B.1.617.1 (India)	Kappa	L452R:E484Q	No Change[d]	No Change[d]	5.1	2.0-5.0
C.37 (Peru)	Lambda	L452Q:F490S	No Change[d]	ND	1.1	ND
B.1.621 (Colombia)	Mu	R346K:E484K:N501Y	7.5-fold	ND	13.5	ND
B.1.427 / B.1.429 (United States)	Epsilon	L452R	No Change[d]	No Change[d]	1.2-4.4	5.0-14.0
R.1 (Multiple country)	-	E484K	No Change[d]	ND	4.6	ND
B.1.1.519 (Multiple country)	-	T478K	No Change[d]	ND	2.3	ND
C.36.3 (Multiple country)	–	R346S:L452R	No Change[d]	ND	3.9	ND

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions Tested	Fold Reduction in Susceptibility[a]		IC_{50} (ng/mL)	
Pango Lineage (origin)	WHO Label		Pseudovirus[b]	Authentic SARS-CoV-2[c]	Pseudovirus [b]	Authentic SARS-CoV-2 [c]
B.1.214.2 (Multiple country)	–	Q414K:N450K	No Change[d]	ND	1.6	ND
B.1.619.1 (Multiple country)	–	N440K:E484K	No Change[d]	ND	7.6	ND
P.2 (Brazil)	Zeta	E484K	No Change[d]	ND	10.4	ND
B.1.616 (France)	-	V483A	No Change[d]	ND	1.1	ND
A.23.1 (UK)	-	V367F	No Change[d]	ND	0.5	ND
A.27 (Multiple country)	-	L452R:N501Y	No Change[d]	ND	1.8	ND
AV.1 (Multiple country)	-	N439K:E484K	5.9-fold	ND	13.0	ND

[a] Range of reduced in vitro potency across multiple sets of co-occurring substitutions and/or testing labs using research-grade assays; mean fold change in half maximal inhibitory concentration (IC_{50}) of monoclonal antibody required for a 50% reduction in infection compared to wild type reference strain.

[b] Pseudoviruses 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) harbouring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages.

[c] Authentic SARS-CoV-2 expressing the entire variant spike protein were tested including Alpha (+E484K or S494P) harbouring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages.

[d] No change: <5-fold reduction in susceptibility.

[e] Omicron spike mutations: A67V, H69-, V70-, T95I, G142D, V143-,Y144-, Y145-, N211-,L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F.

ND, not determined; RBD, receptor binding domain.

It is not known how pseudovirus or authentic SARS-CoV-2 neutralisation susceptibility data correlate with clinical outcome.

In research-grade neutralisation assays using recombinant pseudovirus SARS-CoV-2 spike variant strains, tixagevimab and cilgavimab retained activity against Alpha (B.1.1.7), Beta (B.1.351), Epsilon (B.1.427 / B.1.429), Delta (B.1.617.2), and A_1 variants and variants containing corresponding K417N, L452R, T478K, E484K, S494P, N501Y, Q675H, Q677H, P681H or V1176F individual spike substitutions detected in participants who received tixagevimab and cilgavimab.

It is possible that resistance-associated variants to tixagevimab and cilgavimab together could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. Tixagevimab and cilgavimab together retained activity against pseudoviruses harbouring individual SARS-CoV-2 spike substitutions (E484D/K/Q, F490S, Q493R, S494P, K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, F486V, and Q493K) identified in neutralisation escape variants of other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein.

Pharmacodynamics

Evaluation of EVUSHELD over a dose range of 300-3000 mg through intravenous (IV) administration established a dose-dependent exposure relationship of neutralising antibody titer. In a Phase I study, following a single 300 mg IM dose of EVUSHELD in healthy volunteers (N= 10) neutralising antibodies geometric mean titers (GMT) at 7, 30, 60, 90, 150, 210 and 270 days post-dose were 689.2, 852.8, 656.8, 533.7, 290.1, 297.5 and 98.6 respectively, which are similar to the increases observed in participants receiving 300 mg IV.

In PROVENT, following a single 300 mg IM dose of EVUSHELD, neutralising antibody GMT at 7, 28, 57, and 91 days post-dose were similar to those observed in the Phase I healthy volunteer study and were 16, 22, 17 and 12-fold higher, respectively, than the GMT measured in convalescent plasma from COVID-19 patients (GMT= 30.8).

Clinical trials

Prophylaxis of COVID-19

PROVENT

PROVENT is an ongoing Phase III, randomised (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 participants were individuals considered to be at increased risk for inadequate response to active immunisation (due to age ≥60 years, co-morbidity, pre-existing chronic illness, immunocompromised, or intolerant of vaccination) or at increased risk of SARS-CoV-2 infection (due to their location or circumstances at time of enrolment). Participants received either a single dose (administered as two IM injections) of EVUSHELD 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab administered separately) or placebo. The study excluded participants with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Individuals who have previously received a COVID-19 vaccine were also excluded. 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 well balanced across the EVUSHELD and placebo arms. The median age was 57 years (with 24% of participants aged 65 years or older and 4% of participants aged 75 years or older), 46% of participants were female, 73% were White, 3.3% 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%).

The primary analysis included 5172 participants who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3441 received EVUSHELD and 1731 received placebo. 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.

EVUSHELD significantly (p-value <0.001) reduced the risk of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19), compared to placebo (Table 7). At the time of data cut-off for the primary analysis, the median follow-up time post-administration was 83 days (range 3 to 166 days).

Table 7 Incidence of COVID-19 (Full Pre-Exposure Analysis Set)

	N	Number of events[a], n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD 300 mg[b]	3441	8 (0.2%)	77 % (46 - 90)
Placebo	1731	17 (1.0%)	

CI = Confidence Interval, N = number of participants in analysis.

[a] Primary endpoint, a participant 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.

[b] 300 mg (150 mg tixagevimab and 150 mg cilgavimab).

Efficacy was consistent across pre-defined sub-groups including age, gender, ethnicity, baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19 and at increased risk for inadequate response to active immunisation.

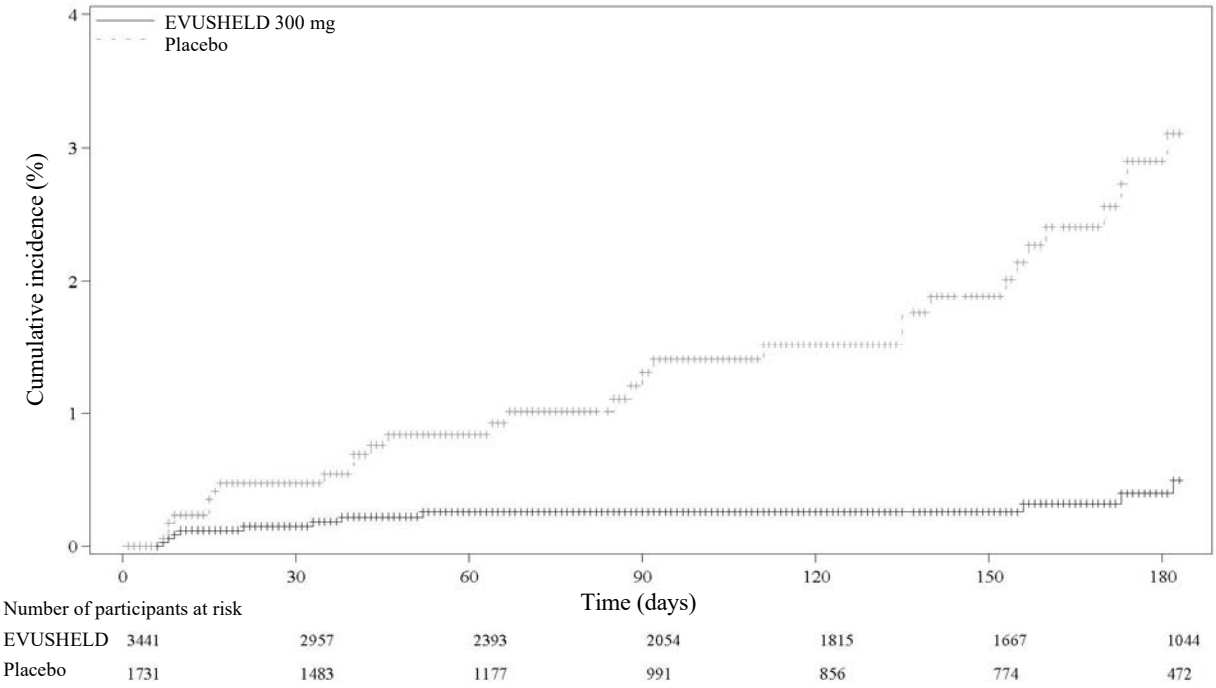
There was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause for participants who had received EVUSHELD (12/3441) compared with placebo (19/1731), relative risk reduction 69% (95% CI: 36, 85); p-value= 0.002.

Efficacy was assessed in participants who had no serological evidence, at baseline, of previous SARS-CoV-2 infection (SARS-CoV-2 nucleocapsid antibody negative). EVUSHELD significantly reduced the risk of any SARS-CoV-2 infection (symptomatic or asymptomatic, SARS-CoV-2 nucleocapsid antibody positive at any time post-baseline) when compared to placebo; with SARS-CoV-2 nucleocapsid antibodies observed in 0.7% (21/3123) of participants who received EVUSHELD and 1.3% (21/1564) of participants who received placebo (relative risk reduction 51%, 95% CI: 11, 73; p-value= 0.020).

At the primary data cut-off, among participants who received EVUSHELD there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR-positive symptomatic illness characterised by a minimum of either pneumonia [fever, cough, tachypnoea or dyspnoea, 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 participants who received placebo.

An additional data cut-off was conducted to provide post-hoc updated safety and efficacy analyses; the median follow-up was 6.5 months for participants in both the EVUSHELD and placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 83% (95% CI 66-91), with 11/3441 [0.3%] events in the EVUSHELD arm and 31/1731 [1.8%] events in the placebo arm, see Figure 1). These results are consistent with the duration of protection predicted by population pharmacokinetic (PK) modelling (see Section 5.2 Pharmacokinetic properties). At a median follow-up of 6.5 months, among participants who received EVUSHELD there were no severe/critical COVID-19 events compared to five events among participants who received placebo.

Figure 1 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19



At the primary DCO, illness visit sequencing data was available for 21 participants with COVID-19 infection (6 who received tixagevimab and cilgavimab and 15 placebo). At an allele fraction ≥ 25%, 14 participants were infected with variants of concern or variants of interest, including 8 participants with Alpha (B.1.1.7) (8 placebo), 1 participant with Beta (B.1.351) (1 who received tixagevimab and cilgavimab), 3 participants with Delta (B.1.617.2) (3 placebo), and 2 participants with Epsilon (B.1.429) (2 who received tixagevimab and cilgavimab). Seven additional participants 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 an allele fraction ≥3% included V503F in the tixagevimab and cilgavimab group.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional between 300 mg and 3000 mg following a single IV administration.

Absorption

After a single 300 mg IM dose (150 mg each antibody) in healthy volunteers, the mean (%CV) maximum concentration (C_{max}) was 16.5 (35.6%) and 15.3 (38.5%) µg/mL for tixagevimab and cilgavimab respectively which was reached at a median T_{max} of 14 days. The estimated absolute bioavailability after a single 150 mg IM dose was 68.5% for tixagevimab and 65.8% for cilgavimab.

Based on pharmacokinetic/pharmacodynamic modelling, the time to achieve the minimum protective serum concentration (2.2 µg/mL) is estimated to be 6 hours following 300 mg IM administration into the gluteal region.

Distribution

Based on PK modelling, the central volume of distribution was 2.72 L for tixagevimab and 2.48 L for cilgavimab. The peripheral volume of distribution was 2.64 L for tixagevimab and 2.57 L for cilgavimab.

Biotransformation/Metabolism

Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Excretion

The clearance (CL) was 0.041 L/day for tixagevimab and 0.041 L/day for cilgavimab with between subject variability of 21% and 29% respectively. The estimated population median terminal elimination half-life was 89 days for tixagevimab and 84 days for cilgavimab.

In PROVENT, following a single 300 mg IM dose of EVUSHELD, the mean serum concentration was 26.7 µg/mL (SD: 11.2) on Day 29. Based on population PK modelling and the strong correlation between serum concentrations and neutralising antibody titer over time, the duration of protection following pre-exposure prophylactic administration of a single 300 mg dose of EVUSHELD is estimated to be at least 6 months.

Special populations

Renal impairment

No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of tixagevimab and cilgavimab.

Tixagevimab and cilgavimab are not eliminated intact in the urine, since monoclonal antibodies with molecular weight >69 kDa do not undergo renal elimination, thus renal impairment is not expected to significantly affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

Based on population PK analysis, there is no difference in the clearance of tixagevimab and cilgavimab in patients with mild (N=978) or moderate (N=174) renal impairment compared to patients with normal renal function. In the population PK model there were insufficient participants with severe renal impairment (N=21) to draw conclusions.

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.

Tixagevimab and cilgavimab are expected to be catabolised by multiple tissues through proteolytic degradation into amino acids and recycling into other proteins, therefore hepatic impairment is not expected to affect the exposure of tixagevimab and cilgavimab.

Elderly patients

Of the 2560 participants in the pooled PK analysis, 21% (N= 534) were 65 years of age or older and 4.2% (N= 107) 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 individuals.

Paediatric population

The PK of tixagevimab and cilgavimab in individuals <18 years old have not been evaluated.

Using population PK modelling and simulation, the recommended dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in paediatric individuals ages 12 years or older who weigh at least 40 kg as observed in adult individuals, since adults with similar body weight have been included in the clinical trials PROVENT.

Other special populations

Based on a population PK analysis, sex, age, BMI (range 21-41), weight (range 36-177 kg), race, ethnicity, cardiovascular disease, diabetes and immunocompromise status had no clinically relevant effect on the PK of tixagevimab and cilgavimab.

Drug-Drug Interaction

Tixagevimab and cilgavimab are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Based on PK modelling, vaccination following EVUSHELD administration had no clinically relevant impact on the clearance of EVUSHELD.

No data are available on the clearance of EVUSHELD, if administered following vaccination.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted with EVUSHELD.

Carcinogenicity

No studies have been conducted with EVUSHELD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine
Histidine hydrochloride monohydrate
Sucrose
Polysorbate 80
Water for injection

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C to 8°C).

Do not freeze. Do not shake.

Keep the vials in the original carton to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Each carton contains two vials:

Tixagevimab

1.5 mL of solution for injection in a clear glass vial closed by chlorobutyl elastomeric stopper sealed with a dark-grey aluminium flip-off top.

Cilgavimab

1.5 mL of solution for injection in a clear glass vial closed by chlorobutyl elastomeric stopper sealed with a white aluminium flip-off top.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Tixagevimab and cilgavimab are two human immunoglobulin(IgG1κ) monoclonal antibodies produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

CAS number

Tixagevimab: 2420564-02-7

Cilgavimab: 2420563-99-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

For EVUSHELD enquiries contact 1800 805 342 or visit www.laab.azcovid-19.com

9 DATE OF FIRST APPROVAL

26 February 2022

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	New product

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