NEW ZEALAND DATA SHEET

1. PRODUCT NAME

EVUSHELD; 150 mg + 150 mg; solution for injection

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).

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

For the full list of excipients see section 6.1.

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 has provisional consent (see section 5.1) for the following indication below:

EVUSHELD is indicated 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 sections 4.2, 5.1 and 5.2.

4.2 DOSE AND METHOD OF ADMINISTRATION

Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be observed after administration according to local medical practice

Dose

The recommended dose in adults and adolescents aged 12 years and older weighing at least 40 kg is 150 mg of tixagevimab and 150 mg of cilgavimab, administered as two separate sequential intramuscular injections.

There are no safety and efficacy data available on repeat dosing.

Special patient populations

Elderly

No dose adjustment is required (see section 5.2).

Renal Impairment

No dose adjustment is required (see section 5.2).

Hepatic Impairment

No dose adjustment is required (see section 5.2).

Paediatric population

No dose adjustment is required in adolescents aged 12 years and older weighing at least 40 kg (see section 5.2). The safety and efficacy of EVUSHELD in children under 12 years of age have not yet been established. No data are available.

Method of administration

For intramuscular injection.

Tixagevimab and cilgavimab must be given as separate sequential intramuscular injections at different injection sites in two different muscles, preferably in the gluteal muscles.

Each carton of EVUSHELD contains two vials:

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

Table 1 Dosage of tixagevimab and cilgavimab

EVUSHELD dose (tixagevimab + cilgavimab)	**Antibody dose**	**Number of vials needed†**	**Volume to withdraw from vial(s)**
150 mg + 150 mg	tixagevimab 150 mg	1 vial (dark grey cap)	1.5 mL
	cilgavimab 150 mg	1 vial (white cap)	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. 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been reported following administration of EVUSHELD (see section 4.8). 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/or thrombo-embolic events

In the PROVENT study, participants in the EVUSHELD arm experienced more serious cardiovascular adverse events compared to those in the placebo arm (0.7% versus 0.3%), notably coronary events (e.g myocardial infarction). A smaller imbalance has been observed for thrombo-embolic events (0.8% versus 0.6%), notably pulmonary embolism. The majority of subjects had cardiovascular risk factors and/or history of cardiovascular disease that could explain the occurrence of such events. A causal relationship between EVUSHELD and these events has not been established.

The risks and benefits should be considered prior to initiating EVUSHELD in individuals at high risk for cardiovascular or thrombo-embolic events. Patients should be advised of signs or symptoms suggestive of cardiovascular event (notably chest pain, dyspnoea, malaise, feeling lightheaded or faint) and to seek immediate medical attention if such symptoms occur.

Breakthrough infection or treatment failure due to antiviral resistance

The clinical trials with Evusheld were conducted when Alpha, Beta, Gamma and Delta variants were predominant. Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of Evusheld. Evusheld may not be effective at preventing or treating COVID-19 caused by these SARS-CoV-2 viral variants. The *in-vitro* neutralisation activity of EVUSHELD against SARS-CoV-2 viral variants are shown in Table 3 (see section 5.1).

Patients who receive EVUSHELD prophylactically should be informed of the potential for breakthrough infections to occur due to the development of viral variants that are resistant to tixagevimab and cilgavimab. Patients should be instructed to promptly seek medical advice if signs or symptoms of COVID-19 occur (the most common symptoms include fever, cough, tiredness and loss of taste or smell; the most serious symptoms include difficulty breathing or shortness of breath, loss of speech or mobility, or confusion and chest pain).

Decisions regarding the use of EVUSHELD for the treatment of COVID-19 should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viral variants, including geographical prevalence and local guidelines.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No interaction studies have been conducted.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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 foetal 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.

Breast-feeding

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.

Fertility

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

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 UNDESIRABLE EFFECTS

Summary of the safety profile

A total of 4,210 adult participants have received 150 mg tixagevimab and 150 mg cilgavimab, via intramuscular injection, in Phase III prophylaxis studies.

The most common adverse reactions were injection site reactions (1.3%).

Adverse Reactions

Adverse Reactions in 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 are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (cannot be estimated from available data).

Table 2 Tabulated list of adverse reactions

MedDRA system organ class	Adverse reaction	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).

Summary of post-authorisation/marketing data

The following adverse reaction has been identified during post-authorisation/-marketing use of EVUSHELD. It is generally not possible to reliably determine the frequency because such reactions have been reported spontaneously from a population of uncertain size. The frequency of these adverse reactions is therefore 'not known' (cannot be estimated from available data).

Immune system disorders:

- Serious hypersensitivity including anaphylaxis, see section 4.4.

Paediatric population

No data are available for paediatric patients <18 years old (See Sections 4.2 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies, ATC code: J06BD03

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 protein with equilibrium dissociation constants of K_D = 2.76 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.

Antibody dependent enhancement (ADE) of infection

The potential of tixagevimab and cilgavimab to mediate antibody-dependent viral entry was assessed in FcγRII-expressing Raji cells co-incubated with recombinant virus 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 $TCID_{50}$ 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

SARS-CoV-2 or recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein were serially passaged in cell cultures in the presence of cilgavimab or tixagevimab individually, or tixagevimab and cilgavimab in combination. Escape variants were identified following passage with cilgavimab, but not with tixagevimab 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.

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.

Neutralisation activity of EVUSHELD against pseudovirus and/or live virus SARS-CoV-2 variant strains are shown in Table 3. 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 3 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		Pseudoviruses[b]	Authentic SARS-CoV-2[c]	Pseudovirus[b]	Authentic SARS-CoV-2[c]
B.1.1.7 (UK)	Alpha	N501Y	No Change[d]	No Change[d]	1.1-9.0	4-39.5
B.1.351 (South Africa)	Beta	K417N:E484K: N501Y	No Change[d]	No Change[d]	5.6-11.4	6.5-256
P.1 (Brazil)	Gamma	K417T:E484K: N501Y	No Change[d]	No Change[d]	1.8-2.7	3.2-8
B.1.617.2 (India)	Delta	L452R:T478K	No Change[d]	No Change[d]	1.9-2.2	3-7.5
AY.1/AY.2 (India)	Delta [+K417 N]	K417N:L452R: T478K	No Change[d]	ND	1.9	ND
B.1.1.529 (South Africa)	Omicron BA.1	All identified[e]	132- to 183-fold	12- to 30-fold	51-277	147–278

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions Tested	Fold Reduction in Susceptibility[a]		IC_{50} (ng/mL)	
Pango Lineage (origin)	WHO Label		Pseudoviruses[b]	Authentic SARS-CoV-2[c]	Pseudovirus[b]	Authentic SARS-CoV-2[c]
BA.1.1 (Multiple country)	Omicron BA.1.1	G339D:R346K: S371L:S373P: S375F:K417N: N440K:G446S: S477N:T478K: E484A:Q493R: G496S:Q489R: N501Y:Y505H	424 fold	176 fold	466	1147
BA.2 (Multiple country)	Omicron BA.2	G339D:S371F: S373P:S375F: T376A:D405N: R408S:K417N: N440K:S477N: T478K:E484A: Q493R:Q498R: N501Y:Y505H:	No Change[d]	No Change[d]	9.8	35
BA.2.12.1 (United States)	Omicron BA.2.12.1	G339D:S371F:S373P: S375F:T376A:D405N:R 408S:K417N:N440K:L45 2Q:S477N T478K:E484A:Q493R:Q 498R:N501Y:Y505H	No Changed	ND	10.7	ND
BA.2.75 (India)	Omicron BA.2.75	G339H:S371F:S373P: S375F:T376A:D405N:R 408S:K417N:N440K:G4 46S:N460K:S477N:T478 K:E484A:Q498R:N501Y: Y505H	2.4- to 15 fold	ND	1.2-14	ND
BA.2.75.2 (India)	Omicron BA.2.75.2	BA.2.75+ R346T:F486S	>5000-fold[f]	ND	> 10000[f]	ND
BA.3 (Multiple country)	Omicron BA.3	G339D: S371F:S373P: S375F:D405N:K417N:N 440K:G446S:S477N:T47 8K:E484A:Q493R:Q498 R:N501Y:Y505H	16-fold	ND	34.5	ND
BA.4 (Multiple country)	Omicron BA.4	G339D:S371F:S373P: S375F:T376A:D405N:R 408S:K417N:N440K:L45 2R:S477N:T478K:E484 A:F486V:Q498R:N501Y: Y505H	33- to 65-fold	ND	65-69.4	ND
BA.4.6 (United States)	Omicron BA.4.6	G339D:R346T:S371F:S 373P:S375F:T376A:D40 5N:R408S:K417N:N440 K:L452R:S477N:T478K: E484A:F486V:Q498R:N 501Y:Y505H	>1000-fold[f]	ND	>1000[f]	ND
BA.5 (Multiple country)	Omicron BA.5	G339D:S371F:S373P: S375F:T376A:D405N: R408S:K417N:N440K: L452R:S477N:T478K: E484A:F486V:Q498R: N501Y:Y505H	33- to 65 fold	2.8- to 16 fold	65-69.4	56.6-229
BF.7 (United States/ Belgium)	Omicron BF.7	BA.4+ R346T	>5000-fold[f]	ND	>10000[f]	ND
BJ.1 (Multiple country)	Omicron BJ.1	G339H:R346T:L368I: S371F:S373:S375F: T376A:D405N:R408S: K417N:N440K:V445P: G446S:S477N:T478K: V483A:E484A:F490V: Q493R:Q498R:N501Y: Y505H	228 to 424--fold	ND	228-848	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]
BQ.1 (Nigeria)	Omicron BQ.1	BA.5+ K444T:N460K	>2000-fold[f]	ND	>10000[f]	ND
BQ.1.1 (Multiple country)	Omicron BQ.1.1	BA.5+ R346T:K444T:N460K	>2000-fold[f]	ND	>10000[f]	ND
BN.1 (Multiple country)	Omicron BN.1	G339D:R346T:K356T:S371F:S373P:S375F:D405N:R408S:K417N:N440K:G446S:N460K:S477N:T478K:E484A:F490S:Q493R:Q498R:Y505H	68-fold	ND	61-68	ND
XBB (Multiple country)	Omicron XBB	G339H:R346T:L368I:S371F: S373P:S375F:T376A:D405N:R408S:K417N:N440K:V445P:G446S:N460K:S477N:T478K:E484A:F486S:F490S:Q498R:N501Y:Y505H	>1400-fold[f]	ND	>1000 f	ND
XBB.1.5	Omicron XBB.1.5	G339H+R346T+L368I+S371F+S373P+S375F+T376A+D405N+R408S+K417N+N440K+V445P+G446S+N460K+S477N+T478K+E484A+F486P+F490S+Q498R+N501Y+Y505H	> 5,000[f] fold	ND	> 10,000[f]	ND
B.1.525 (Multiple country)	Eta	E484K	No Change[d]	ND	5-9.5	ND
B.1.526 (United States)	Iota	E484K	No Change[d]	No Change[d]	1.9-5.2	1.0-7.0
B.1.617.1 (India)	Kappa	L452R:E484Q	No Change[d]	No Change[d]	2.5-5.1	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	No Change[d]	ND	17.3	ND
B.1.427 / B.1.429 (United States)	Epsilon	L452R	No Change[d]	No Change[d]	1.0-4.5	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
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	1.1-1.2	ND
A.23.1 (UK)	-	V367F	No Change[d]	ND	0.5	ND

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions Tested	Fold Reduction in Susceptibility[a]		IC_{50} (ng/mL)	
Pango Lineage (origin)	WHO Label		Pseudoviruses[b]	Authentic SARS-CoV-2[c]	Pseudovirus[b]	Authentic SARS-CoV-2[c]
A.27 (Multiple country)	-	L452R:N501Y	No Change[d]	ND	1.8	ND
AV.1 (Multiple country)	-	N439K:E484K	No Change[d]	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: <10-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.

[f] Tixagevimab and cilgavimab together are unlikely to be active against this variant.

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 PROVENT, 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.

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

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.

Pharmacodynamic effects

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 Efficacy and Safety

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.

The baseline demographics were well balanced across the EVUSHELD and placebo arms. The median age was 57 years (with 43% of participants aged 60 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 5197 participants, 78% had baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19, including immunosuppressive disease, immunosuppressive medications, diabetes, severe obesity, cardiac disease, chronic obstructive pulmonary disease, chronic kidney disease and chronic liver disease.

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. EVUSHELD significantly (p-value <0.001) reduced the risk of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) when compared to placebo (Table 4). The median follow-up time post-administration was 83 days.

Table 4 Incidence of COVID-19

	N	Number of events[a], n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD[b]	3 441	8 (0.2%)	77% (46 - 90)
Placebo	1 731	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] 150 mg tixagevimab and 150 mg cilgavimab.

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

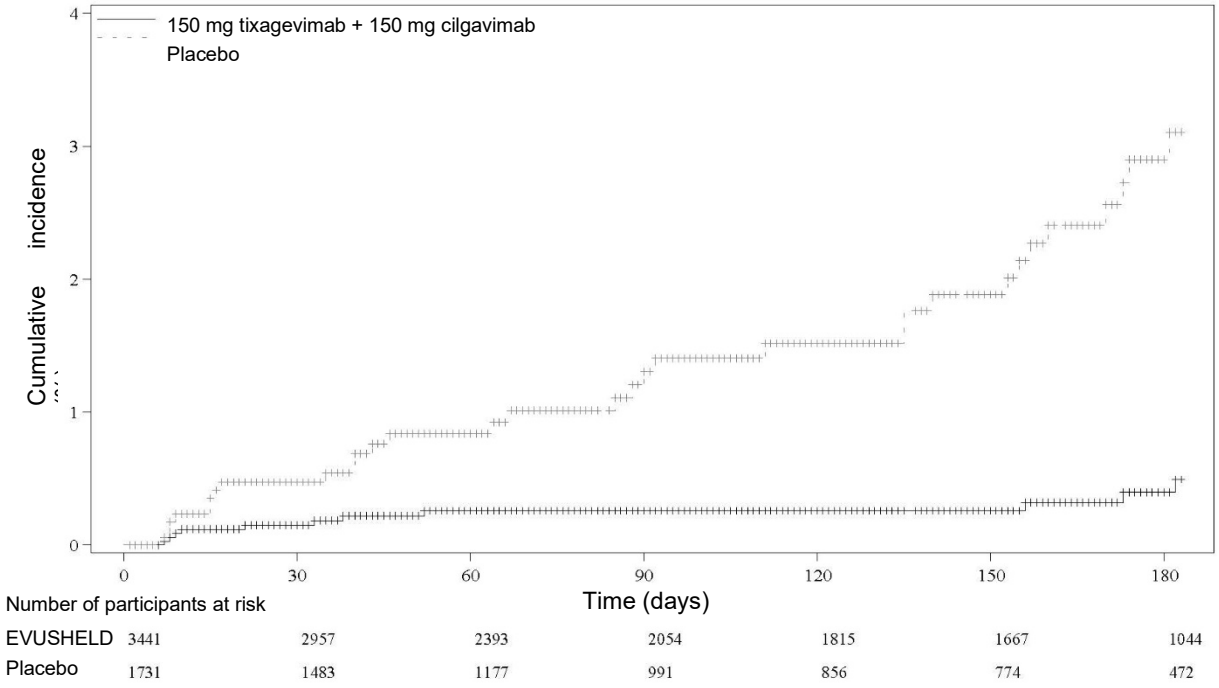
There was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause for participants who had received EVUSHELD (12/3441) compared with placebo (19/1731), relative risk reduction 69% (95% CI: 36, 85); p-value= 0.002.

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).

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 EVUSHELD 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). 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



The predominant SARS-CoV-2 variants in circulation for the time period represented in Figure 1 were Alpha, Beta, Gamma, Epsilon and Delta. Based on the incidence of primary endpoint events, the duration of efficacy was 6 months.

STORM CHASER

STORM CHASER is an ongoing Phase III randomised (2:1), double-blind, placebo-controlled clinical trial of EVUSHELD for the post-exposure prophylaxis of COVID-19 in adults ≥18 years of age. Enrolled participants were at appreciable risk of imminently developing COVID-19 following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Participants received 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.

The baseline demographics were well balanced across the EVUSHELD and placebo arms. The median age was 48 years (with 20% of participants aged 60 years or older), 49% of the participants were female, 84% were White, 10% were Black/African American, 2.5% were Asian and 58% were Hispanic/Latino.

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

The primary efficacy endpoint, the incidence a participant's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post-dose and before Day 183, was not met. In the overall population, EVUSHELD reduced the risk of developing symptomatic COVID-19 by 33% (95% CI: -26, 65) compared to placebo, which was not statistically significant; with 23 cases of symptomatic COVID-19 in the EVUSHELD arm (3.1%) and 17 cases in the placebo arm (4.6%).

At the primary analysis, based on a Kaplan-Meier estimate of the time to first SARS-CoV-2 RT-PCR-positive symptomatic illness, in participants who received EVUSHELD there were no cases of SARS-CoV-2 RT-PCR-positive symptomatic illness after Day 11, compared to 5 cases in participants who received placebo (these cases are likely to reflect a new exposure to the SARS-CoV-2 virus that occurred after administration).

In pre-planned subgroup analysis by SARS-CoV-2 RT-PCR status at baseline (N = 1073), detectable virus (RT-PCR-positive) versus no detectable virus (RT-PCR-negative or missing), EVUSHELD reduced the risk of developing symptomatic COVID-19 by 73% (95% CI: 27, 90) in participants who were RT-PCR-negative/missing at time of dosing when compared with placebo, with 6/715 cases in the EVUSHELD arm (0.8%) and 11/358 cases in the placebo arm (3.1%).

This medicine has been given a provisional consent under Section 23 of the Act. This means that further evidence on this medicine is awaited or that there are specific conditions of use. Refer to the consent notice published in the New Zealand Gazette for the specific conditions.

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.

Elimination

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 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

Of the 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 has 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 adolescents aged 12 years or older who weigh at least 40 kg as observed in adults, since adults with similar body weight have been included in the clinical trials PROVENT and STORM CHASER .

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 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, COVID-19 vaccination following EVUSHELD administration had no clinically relevant impact on the clearance of EVUSHELD.

5.3 PRECLINICAL SAFETY DATA

Carcinogenesis, mutagenesis, and reproductive toxicology studies have not been conducted.

Non-clinical data reveal no special hazards for humans based on studies of tissue binding and a single-dose toxicity study in cynomolgus monkeys including assessment of safety pharmacology and local tolerance.

In a single-dose toxicology study in cynomolgus monkeys, EVUSHELD administered via IV infusion of 600 mg/kg (combination of 300 mg/kg of tixagevimab and 300 mg/kg of cilgavimab) or an IM injection of 150 mg/kg (75 mg/kg of each antibody) had no adverse effects.

In tissue cross reactivity studies using human adult and foetal tissues no binding was detected.

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

Unopened vial

30 months

Prepared syringes

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

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6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Do not shake.
Store in the original package in order 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 AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

29 July 2022

10. DATE OF REVISION OF THE TEXT

20 March 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Serious hypersensitivity section is updated. Section added regarding breakthrough infection is added.
4.8	Serious hypersensitivity including anaphylaxis is added.

5.1	Antiviral resistance update. Immunogenicity section added. Clinical Efficacy and Safety updated.
6.3	Shelf-life updated.