ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EVUSHELD 150 mg + 150 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each carton contains two vials:

Each vial of tixagevimab contains 150 mg of tixagevimab in 1.5 mL (100 mg/mL).
Each vial of cilgavimab contains 150 mg of cilgavimab in 1.5 mL (100 mg/mL).

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

Excipient with known effect

Each vial of tixagevimab contains 0.6 mg of polysorbate 80.
Each vial of cilgavimab contains 0.6 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pre-exposure prophylaxis
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 (see sections 4.2, 5.1 and 5.2).

Treatment
EVUSHELD is indicated for the treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (see sections 4.2, 5.1 and 5.2).

4.2 Posology and method of administration

EVUSHELD must be administered by a healthcare professional.

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.

Posology

Pre-exposure prophylaxis
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 (Table 1), administered as two separate sequential intramuscular injections.

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

Due to the observed decrease in *in-vitro* neutralisation activity, the duration of protection of EVUSHELD for some variants is uncertain (see section 4.4 and 5.1).

Treatment
The recommended dose in adults and adolescents aged 12 years and older weighing at least 40 kg is 300 mg of tixagevimab and 300 mg of cilgavimab (Table 1), administered as two separate sequential intramuscular injections.

EVUSHELD should be given as soon as possible after a positive viral test for SARS-CoV-2 and within 7 days of the onset of symptoms of COVID-19 (see section 5.1).

Table 1 Recommended dose

Indication	**EVUSHELD dose** tixagevimab + cilgavimab	**Antibody dose**	**Number of vials needed**[a]	**Volume to withdraw from vial**
Pre-exposure prophylaxis	150 mg + 150 mg (1 EVUSHELD carton)	tixagevimab 150 mg	1 vial (dark grey cap)	1.5 mL
		cilgavimab 150 mg	1 vial (white cap)	1.5 mL
Treatment	300 mg + 300 mg (2 EVUSHELD cartons)	tixagevimab 300 mg	2 vials (dark grey cap)	3.0 mL
		cilgavimab 300 mg	2 vials (white cap)	3.0 mL

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

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 two separate sequential intramuscular injections at different injection sites in two different muscles, preferably in the gluteal muscles.

Each carton contains two vials:
- tixagevimab solution for injection (dark grey cap);
- cilgavimab solution for injection (white cap).

For handling instructions of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

Cardiovascular and/or thrombo-embolic events

In the PROVENT study, more participants in the EVUSHELD arm experienced serious cardiac or thromboembolic adverse events as compared to those in the placebo arm (1.6% versus 0.9%). The majority of participants 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.

Clinically significant bleeding disorders

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

Antiviral resistance

The clinical trials with EVUSHELD were conducted when Alpha, Beta, Gamma and Delta variants were predominant. Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies such as tixagevimab and cilgavimab. The *in-vitro* neutralisation activity of EVUSHELD against SARS-CoV-2 viral variants are shown in Table 3 (see section 5.1).

Patients who received EVUSHELD prophylactically should be informed of the potential for breakthrough infections to occur.

The duration of protection for variants with an observed decrease in *in-vitro* neutralisation activity is uncertain.

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.

COVID-19 vaccines

Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

Excipient with known effect

This medicinal product contains 0.6 mg of polysorbate 80 in each vial of tixagevimab and in each vial of cilgavimab. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

No human interaction studies have been performed.

EVUSHELD is not expected to undergo metabolism by hepatic enzymes or renal elimination. Tixagevimab and cilgavimab are not renally excreted or metabolised by cytochrome P450 (CYP) enzymes; therefore, interactions with medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

Based on pharmacokinetic (PK) modelling, COVID-19 vaccination following EVUSHELD administration had no clinically relevant impact on the clearance of EVUSHELD.

Based on PK modelling, immunocompromised condition had no clinically relevant impact on the clearance of EVUSHELD.

Pharmacodynamic interactions

No human interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or 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 (see section 5.3). In tissue cross reactivity studies with tixagevimab and cilgavimab using human foetal tissues no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placenta therefore tixagevimab and cilgavimab have the potential to be transferred from the mother to the developing foetus. The potential treatment benefit or risk of placental transfer of tixagevimab and cilgavimab to the developing foetus is not known.

EVUSHELD should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

It is not known whether tixagevimab and cilgavimab are excreted in human milk but maternal IgG is known to be transferred to milk during the first days after birth.

As tixagevimab and cilgavimab directly target the spike protein of SARS-CoV-2, and in view of low systemic absorption after oral ingestion of antibodies, administration of EVUSHELD whilst breast-feeding can be considered when clinically indicated.

Fertility

There are no data on the effects of tixagevimab and cilgavimab on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

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 the Phase III prophylaxis development program (including PROVENT). The most common adverse reactions (≥ 1%) were injection site reactions (1.6%) and hypersensitivity (1.0%).

A total of 452 non-hospitalised adult patients with mild to moderate COVID-19 have received 300 mg tixagevimab and 300 mg cilgavimab, via intramuscular injection, in TACKLE. The overall safety profile was similar to that reported in participants who received 150 mg tixagevimab and 150 mg cilgavimab in the prophylaxis studies. The most common adverse reaction (≥ 1%) was injection site reaction (2.4%).

Tabulated list of adverse reactions

The adverse reactions in Table 2 are listed by MedDRA system organ class and frequency. 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[a]
Immune system disorders	Hypersensitivity[b]	Common
	Anaphylaxis[c]	Rare
General disorders and administration site conditions	Injection related reaction[d]	Uncommon
Injury, poisoning and procedural complications	Injection site reaction[e]	Common

[a] Frequencies are based on exposure to 150 mg tixagevimab and 150 mg cilgavimab in the pooled data from the prophylaxis studies.
[b] Including the preferred terms Rash and Urticaria.
[c] Identified from post-marketing/post-authorisation reports (see section 4.4).
[d] Description of events reported under the preferred term Injection related reaction include headache, chills and redness, discomfort or soreness near where the injection was given.
[e] Including the preferred terms Injection site pain, Injection site erythema, Injection site pruritus, Injection site reaction and Injection site induration.

Paediatric population
No data are available for paediatric patients < 18 years old (see section 4.2 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for overdose with tixagevimab and cilgavimab. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

In clinical trials, intramuscular doses of up to 300 mg each of tixagevimab and cilgavimab and intravenous doses of up to 1 500 mg each of tixagevimab and cilgavimab have been administered without dose-limiting toxicity.

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 in the Fc regions, to extend antibody half-life and to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease (see section 5.3).

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= 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with the human ACE2 receptor, resulting in a blockade of virus entry. 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* clinically effective serum concentrations of 2.2 µg/mL of EVUSHELD.

Antiviral resistance

SARS-CoV-2 or recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein (pseudovirus) were serially passaged in cell cultures in the presence of tixagevimab or cilgavimab 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.

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 F486S (> 600-fold) and F486V (121- to 149-fold) and variants with reduced susceptibility to cilgavimab alone included those with R346I (> 200-fold), K444E (> 200-fold), K444Q (> 200-fold) and K444R (> 200-fold).

The 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

Pango lineage with spike protein substitutions	Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]		IC_{50} (ng/mL)	
		Pseudovirus[b]	Live Virus[c]	Pseudovirus[b]	Live Virus[c]
Variants of concern					
B.1.1.7 (Alpha, UK)	N501Y	1.0-5.2	0.5-1.4	1.1-9.0	4-39.5
B.1.351 (Beta, South Africa)	K417N:E484K:N501Y	2.5-5.5	0.9-3.8	5.6-11.4	6.5-256
P.1 (Gamma, Brazil)	K417T:E484K:N501Y	0.8-1.7	0.4-2.0	1.8-2.7	3.2-8
B.1.617.2 (Delta, India)	L452R:T478K	1-1.2	0.6-1.0	1.9-2.2	3-7.5
AY.1/AY.2 (Delta [+K417N], India)	K417N:L452R:T478K	1.0	ND	1.9	ND

Pango lineage with spike protein substitutions	Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]		IC_{50} (ng/mL)	
		Pseudovirus[b]	Live Virus[c]	Pseudovirus[b]	Live Virus[c]
B.1.1.529 Omicron, BA.1 (Botswana)	G339D:S371L:S373P: S375F:K417N:N440K: G446S:S477N:T478K: E484A:Q493R:G496S: Q489R:N501Y:Y505H	132-183 [d]	12-30 [d]	51-277 [d]	147-278 [d]
Omicron BA.1.1 (Multiple country)	G339D:R346K:S371L: S373P: S375F:K417N: N440K:G446S:S477N: T478K:E484A:Q493R: G496S:Q489R:N501Y: Y505H	424 [d]	176 [d]	466 [d]	1147 [d]
Omicron BA.2 (Multiple country)	G339D:S371F:S373P: S375F:T376A:D405N: R408S:K417N:N440K:S477 N: T478K:E484A: Q493R:Q498R:N501Y: Y505H:H655Y:N679K:P681 H:N764K	3.2	5.4	9.8	35
Omicron BA.2.12.1 (United States)	G339D:S371F:S373P: S375F:T376A:D405N: R408S:K417N:N440K: L452Q:S477N:T478K:E484A :Q493R:Q498R: N501Y: Y505H	5	ND	10.7	ND
Omicron BA.2.75 (India)	G339H:S371F:S373P: S375F:T376A:D405N:R408S :K417N:N440K:G446S:N460 K:S477N:T478K:E484A:Q49 8R:N501Y:Y505H	2.4-15	ND	1.2-14	ND
Omicron BA.2.75.2 (India)	BA.2.75:R346T:F486S	>5 000 [e]	ND	>10 000 [e]	ND
Omicron BA.3 (Multiple country)	G339D:S371F:S373P: S375F:D405N:K417N: N440K:G446S:S477N: T478K:E484A:Q493R: Q498R:N501Y:Y505H	16	ND	34.5	ND
Omicron BA.4 (Multiple country)	G339D:S371F:S373P: S375F:T376A:D405N: R408S:K417N:N440K: L452R:S477N:T478K: E484A:F486V:Q498R: N501Y:Y505H	33-65 [d]	ND	65-69.4 [d]	ND
Omicron BA.4.6 (United States)	G339D:R346T:S371F: S373P:S375F:T376A: D405N:R408S:K417N:N440 K:L452R:S477N:T478K:E48 4A:F486V:Q498R:N501Y:Y5 05H	>1 000 [e]	ND	>1 000 [e]	ND

Pango lineage with spike protein substitutions	Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]		IC_{50} (ng/mL)	
		Pseudovirus[b]	Live Virus[c]	Pseudovirus[b]	Live Virus[c]
Omicron BA.5 (Multiple country)	G339D:S371F:S373P: S375F:T376A:D405N: R408S:K417N:N440K: L452R:S477N:T478K: E484A:F486V:Q498R: N501Y:Y505H	33-65 [d]	2.8-16 [d]	65-69.4 [d]	56.6-229 [d]
Omicron BF.7 (United States/Belgium)	BA.4:R346T	>5 000 [e]	ND	>10 000 [e]	ND
Omicron BJ.1 (Multiple country)	G339H:R346T:L368I: S371F:S373P:S375F: T376A:D405N:R408S: K417N:N440K:V445P: G446S:S477N:T478K: V483A:E484A:F490V: Q493R:Q498R:N501Y: Y505H	228-424	ND	228-848	ND
Omicron BQ.1 (Nigeria)	BA.5:K444T:N460K	>2 000 [e]	ND	>10 000 [e]	ND
Omicron BQ.1.1 (Multiple country)	BA.5:R346T:K444T:N460K	>2 000 [e]	ND	>10 000 [e]	ND
Omicron BN.1 (Multiple country)	G339D:R346T:K356T:S371F :S373P:S375F:D405N:R408S :K417N:N440K:G446S: N460K:S477N:T478K: E484A:F490S:Q493R:Q498R :Y505H	68	ND	61-68	ND
Omicron XBB (Multiple country)	G339H:R346T:L368I:S371F: S373P:S375F:T376A:D405N: R408S:K417N:N440K: V445P:G446S:N460K:S477N :T478K:E484A:F486S:F490S :Q498R:N501Y:Y505H	>1 400 [e]	ND	>1 600 [e]	ND
XBB.1 (Multiple country)	T19I:del24-26:A27S:V83A: G142D:Y144-:H146Q:Q183E :V213E:G252V:G339H: R346T:L368I:S371F:S373P: S375F:T376A:D405N:R408S :K417N:N440K:V445P: G446S:N460K:S477N:T478K :E484A:F486S:F490S:Q498R :N501Y:Y505H:D614G: H655Y:N679K:P681H: N764K:D796Y:Q954H: N969K	>5 000 [e]	ND	>10 000 [e]	ND

Pango lineage with spike protein substitutions	Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]		IC_{50} (ng/mL)	
		Pseudovirus[b]	Live Virus[c]	Pseudovirus[b]	Live Virus[c]
Omicron XBB.1.5 (Multiple country)	G339H:R346T:L368I:S371F:S373P:S375F:T376A:D405N:R408S:K417N:N440K:V445P:G446S:N460K:S477N:T478K:E484A:F486S:F490S:Q498R:N501Y:Y505H	>5 000 [e]	ND	>10 000 [e]	ND
Omicron XBB.1.16 (India)	T19I:del24-26:A27S:V83A:G142D:Y144-:H146Q:E180V:Q183E:V213E:G252V:G339H:R346T:L368I:S371F:S373P:S375F:T376A:D405N:R408S:K417N:N440K:V445P:G446S:N460K:S477N:T478R:E484A:F486P:F490S:Q498R:N501Y:Y505H:D614G:H655Y:N679K:P681H:N764K:D796Y:Q954H:N969K	>5 000 [e]	ND	>10 000 [e]	ND
Omicron XBB.1.5.10/EG.5 (Multiple country)	XBB.1.5:F456L	>5 000 [e]	ND	10 000 [e]	ND
Omicron EG.5.1 (Multiple country)	XBB.1.5:Q52H:F456L	>5 000 [e]	ND	10 000 [e]	ND
Omicron BA.2.86 (Multiple country)	T19I:R21T:L24-:P25-:P26-:A27S:S50L:H69-:V70-:V127F:G142D:Y144-:F157S:R158G:N211-:L212I:V213G:L216F:H245N:A264D:I332V:G339H:K356T:S371F:S373P:S375F:T376A:R403K:D405N:R408S:K417N:N440K:V445H:G446S:N450D:L452W:N460K:S477N:T478K:N481K:V483-:E484K:F486P:Q498R:N501Y:Y505H:E554K:A570V:D614G:P621S:H655Y:I670V:N679K:P681R:N764K:D796Y:S939F:Q954H:N969K:P1143L	>5 000 [e]	ND	>10 000 [e]	ND

Pango lineage with spike protein substitutions	Characteristic RBD substitutions tested	Fold reduction in susceptibility[a]		IC_{50} (ng/mL)	
		Pseudovirus[b]	Live Virus[c]	Pseudovirus[b]	Live Virus[c]
Omicron JN.1 (Multiple country)	T19I:R21T:L24-:P25-:P26-:A27S:S50L:H69-:V70-:V127F:G142D:Y144-:F157S:R158G:N211-:L212I:V213G:L216F:H245N:A264D:I332V:G339H:K356T:S371F:S373P:S375F:T376A:R403K:D405N:R408S:K417N:N440K:V445H:G446S:N450D:L452W:L455S:N460K:S477N:T478K:N481K:V483-:E484K:F486P:Q498R:N501Y:Y505H:E554K:A570V:D614G:P621S:H655Y:I670V:N679K:P681R:N764K:D796Y:S939F:Q954H:N969K:P1143L	>5 000 [e]	ND	>10 000 [e]	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] The duration of protection for this variant is uncertain.

[e] 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, sequencing data collected at illness visits was available for 21 participants with symptomatic COVID-19 (7 received tixagevimab and cilgavimab, and 14 received placebo). At an allele fraction ≥ 25%, the most commonly observed variants of concern or variants of interest were Alpha (5 total events; all in placebo) and Delta (7 total events; 6 in placebo and 1 in EVUSHELD), with 7 ancestral strain sequences also being observed (3 in placebo and 4 in EVUSHELD).

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.

In TACKLE, baseline visit sequencing data was available for 749 participants (382 received tixagevimab and cilgavimab, and 367 received placebo). At an allele fraction ≥ 25%, the proportion of participants infected with variants of concern or variants of interest was balanced between treatment group, including participants with Alpha, Beta, Gamma, Delta, Lambda and Mu.

Pharmacodynamic effects

In PROVENT, following an intramuscular dose of 150 mg tixagevimab and 150 mg cilgavimab, at Day 8, 29, 58, 92, 183 and 366, the neutralising antibody GMTs were 19, 23, 18, 14, 6, and 3-fold greater, respectively, than the GMT measured in convalescent plasma from COVID-19 patients (GMT= 30.8).

In TACKLE, following a single intramuscular dose of 300 mg of tixagevimab and 300 mg of cilgavimab, greater than 5-fold increase neutralising antibody GMTs were observed in the EVUSHELD group through Day 169 versus the placebo group: 16-, 14-, 22-, 18- and 5.3-fold over placebo at Day 6, 15, 29, 85, and 169, respectively.

Immunogenicity

In PROVENT, following a single EVUSHELD dose (150 mg tixagevimab and 150 mg cilgavimab),treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected in 7.6% (234/3085), 11.3% (341/3024), and 13.1% (403/3086) ADA-evaluable participants who received EVUSHELD.

In TACKLE, following a single EVUSHELD dose (300 mg tixagevimab and 300 mg cilgavimab), treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected in 7.3% (27/372), 12.7% (46/363), and 14.5% (54/373) of ADA-evaluable participants, respectively.

No evidence of an association of ADA with any impact on PK or safety has been observed.

Clinical efficacy

Prophylaxis of COVID-19

PROVENT was a 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. Enrolled 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, for example health care workers including staff for long-term care facilities, working in high risk industrial settings or living with high density proximity, including students in dormitories and military barracks). Participants received either 150 mg of tixagevimab and 150 mg of cilgavimab or placebo, administered as two separate intramuscular injections. 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 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% were Asian, 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5 197 participants, 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 5 172 participants who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3 441 received EVUSHELD and 1 731 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.

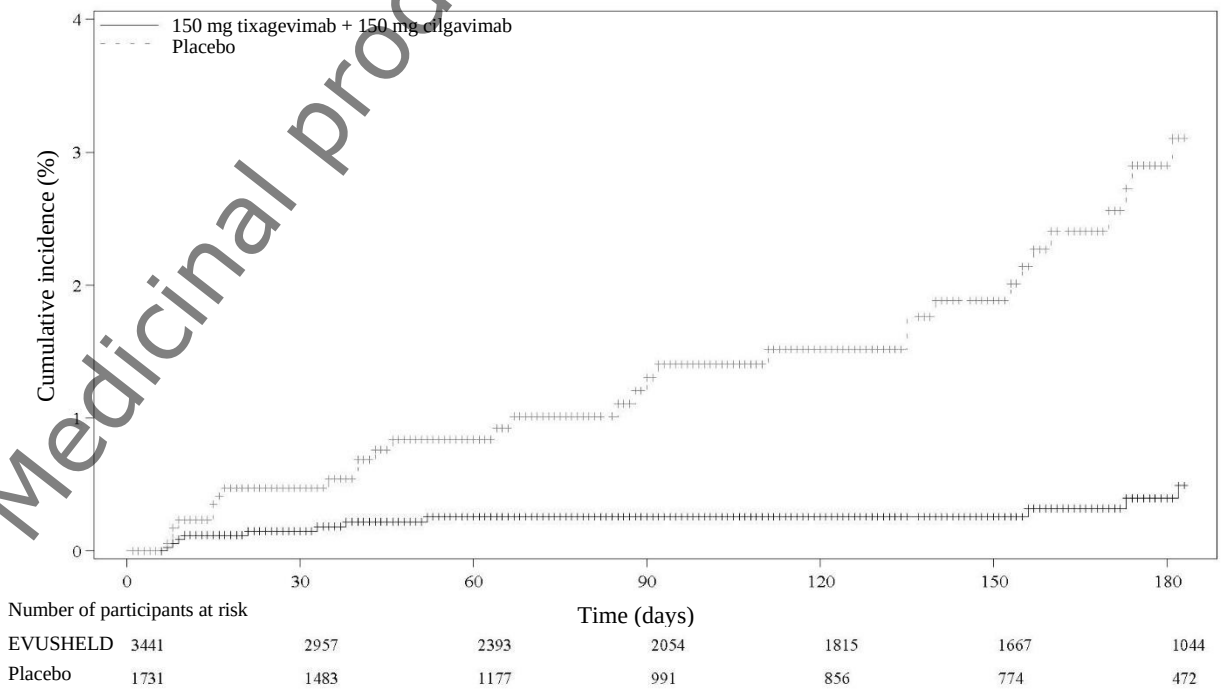
Efficacy was consistent across pre-defined sub-groups including age, gender, ethnicity and baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19.

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 11/3 441 (0.3%) events in the EVUSHELD arm and 31/1 731 (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.

In exploratory analyses of all participants who received EVUSHELD or placebo, including 25 participants who were subsequently found to have been SARS-CoV-2 RT-PCR-positive at baseline, the relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 78% (95% CI 59, 88), with 14/3 460 (0.4%) events in the EVUSHELD arm and 31/1 737 (1.8%) events in the placebo arm at a median follow-up of 6.5 months.

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.

Treatment of mild to moderate COVID-19

TACKLE was a Phase III, randomised (1:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the treatment of adult patients with mild to moderate COVID-19. The study enrolled individuals who had not received COVID-19 vaccination, who were not hospitalised for COVID-19 treatment, and who had at least 1 or more COVID-19 symptom that was at least mild in severity. Treatment was initiated within 3 days of obtaining the sample for a positive SARS-CoV-2 viral infection and within ≤7 days of COVID-19 symptom onset. Patients received standard of care treatment and either 300 mg of tixagevimab and 300 mg of cilgavimab (N= 413) or placebo (N= 421), administered as two separate intramuscular injections. Participants were stratified by time from symptom onset (≤5 days versus >5 days) and risk of progression to severe COVID-19 (high risk versus low risk).

Demographics and disease characteristics were well balanced across the treatment and placebo groups. At baseline, the median age was 46 years (with 13% of subjects aged 65 years or older), 50% of the participants were female, 62% were White, 5.6% were Asian, 4.0% were Black and 52% were Hispanic/Latino. The majority of participants (84%) were seronegative at baseline, and 90% were considered at higher risk of progressing severe COVID-19, defined as either individuals aged 65 years and older at randomisation or individuals aged < 65 years and having at least one medical condition or other factor that placed them at higher risk for progression to severe COVID-19. High risk co-morbidities included: obesity (BMI ≥ 30) (43%), smoking (current or former) (40%), hypertension (28%), chronic lung disease or moderate to severe asthma (12%), diabetes (12%), cardiovascular disease (including history of stroke) (9%), immunocompromised state (from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines) (5%), cancer (4%), chronic kidney disease (2%), or chronic liver disease (2%).

At baseline, 88% of patients had WHO clinical progression scale of 2 and 12% had WHO clinical progression scale of 3 COVID-19, the median duration of symptoms prior to treatment was 5 days.

The primary efficacy endpoint was a composite of either severe COVID-19 or death from any cause by Day 29, in participants who received treatment within 7 days from symptom onset and were not hospitalised at baseline. Severe COVID-19 was defined as characterised by either pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltrates observed on chest X-ray or lung computed tomography scan) or hypoxemia (SpO_2 <90% in room air and/or severe respiratory distress) and a WHO clinical progression scale score of 5 or higher. EVUSHELD demonstrated a statistically significant reduction in severe COVID-19 or death from any cause compared to placebo (Table 5). Given the small sample size, no conclusion can be drawn regarding the efficacy in seropositive patients.

Table 5: Incidence of severe COVID-19 or death from any cause through Day 29

Population	**Treatment**	**N**	**Number of events, n (%)**	**Relative risk reduction, % (95% CI)**	**p-value [a]**
Non-hospitalised patients dosed ≤ 7 days from symptom onset (mFAS)	EVUSHELD[b]	407	18 (4.4%)	50% (15, 71)	p= 0.010
	Placebo	415	37 (8.9%)		

Population	Treatment	N	Number of events, n (%)	Relative risk reduction, % (95% CI)	p-value [a]
All randomised participants, including hospitalised and non-hospitalised patients (FAS)	EVUSHELD[b]	446	24 (5.4%)	42% (5, 64)	p= 0.028
	Placebo	444	41 (9.2%)		

CI = Confidence Interval, N= Number of participants included in analysis, mFAS= Modified full analysis set, FAS= Full analysis set.

a. Results from a CMH test stratified by time from symptom onset (≤ 5 vs. > 5 days), and risk of progression to severe COVID-19 (high vs. low).

b. 300 mg tixagevimab and 300 mg cilgavimab.

Missing response data were not imputed.

The relative risk reduction was 67% (95% CI of 31, 84) in non-hospitalised patients dosed within 5 days of symptom onset (p= 0.002).

The results of the primary composite endpoint were driven by the incidence of severe COVID-19. Up to Day 29, 7 deaths had been reported, 3 in the EVUSHELD arm and 4 in the placebo arm. Of the 7 deaths, 2 were not COVID-19 related. Both of these were in the EVUSHELD arm and contributed to the primary composite endpoint.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with EVUSHELD in one or more subsets of the paediatric population in the prophylaxis and treatment of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional between 150 mg tixagevimab and 150 mg cilgavimab and 1 500 mg of tixagevimab and 1 500 mg of cilgavimab following a single intravenous administration. Population PK analysis of data from healthy volunteers and patients enrolled in three Phase III studies of tixagevimab and cilgavimab in pre-exposure prophylaxis (PROVENT), post-exposure prophylaxis (STORMCHASER) and treatment of mild-to-moderate COVID-19 (TACKLE), as well as data from five additional Phase I and II studies, with doses ranging from 300 mg (150 mg tixagevimab and 150 mg cilgavimab) to 600 mg (300 mg tixagevimab and 300 mg cilgavimab) intramuscular administration and 300 mg (150 mg tixagevimab and 150 mg cilgavimab) to 3 000 mg (1 500 mg tixagevimab and 1 500 mg cilgavimab) intravenous administration supports dose proportionality of tixagevimab, cilgavimab and EVUSHELD.

Absorption

Based on population PK modelling, following a single intramuscular dose of 150 mg tixagevimab and 150 mg cilgavimab the predicted median (90% prediction interval [PI]) maximum serum concentration (C_{max}) of EVUSHELD was 26.9 µg/mL (90% PI: 12.6, 53.7), the median time to reach C_{max} (T_{max}) was 19 days (90% PI: 5, 45).

After a single intramuscular dose of 300 mg tixagevimab and 300 mg cilgavimab the predicted C_{max} of EVUSHELD was 53.9 µg/mL (90% PI: 25.2,107.3), which was reached at a median T_{max} of 19 days (90% PI: 5, 46).

The estimated absolute bioavailability was 67.1% for EVUSHELD, 61.5% for tixagevimab and 65.8% for cilgavimab.

Distribution

Based on PK modelling, the central volume of distribution was 3.17 L for tixagevimab and 3.52 L for cilgavimab. The peripheral volume of distribution was 1.77 L for tixagevimab and 1.82 L for cilgavimab.

Biotransformation

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) median (95% CI) was 0.050 (0.049, 0.052) L/day for EVUSHELD, 0.046 (0.044, 0.047) L/day for tixagevimab and 0.052 (0.049, 0.054) L/day for cilgavimab with interindividual variability of 43%, 41% and 44% respectively. The estimated population median (5^{th} and 95^{th} percentile) terminal elimination half-life was 79 (46, 101) days for EVUSHELD, 81 (49, 106) days for tixagevimab and 78 (49, 97) days for cilgavimab.

Following a single intramuscular dose of 150 mg tixagevimab and 150 mg cilgavimab, the predicted median EVUSHELD serum concentration was 24.5 µg/mL (90% PI: 11.8, 44.8) on Day 29 and 6.2 µg/mL (90% PI: 1.8, 14.7) on Day 183.

Following a single intramuscular dose of 300 mg tixagevimab and 300 mg cilgavimab, the predicted median EVUSHELD serum concentration was 49.1 µg/mL (90% PI: 23.6, 89.5) on Day 29 and 12.5 µg/mL (90% PI: 3.6, 29.3) on Day 183.

There was no clinically relevant difference on the clearance of tixagevimab or cilgavimab between participants with COVID-19 enrolled in TACKLE and those enrolled in the prophylaxis studies.

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, 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 renal impairment (assessed via baseline eGFR and creatinine clearance) compared to patients with normal renal function. In the population PK model there were insufficient participants with severe renal impairment 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 expected to be low.

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, 17.6% (N= 871) were 65 years of age or older and 3.2% (N= 156) 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 prophylaxis and treatment clinical trials.

High body weight
Based on population PK analysis, a decrease in EVUSHELD maximum serum concentration and concentration at 6 months was observed with increased body weight. The maximum serum concentration and concentration at 6 months in an adult weighing 108 kg (87.5 percentile) were both predicted to be approximately 24% lower than in an adult weighing 81 kg (median).

Other special populations
Based on a population PK analysis, sex, age, race, ethnicity, cardiovascular disease, diabetes and immunocompromise had no clinically relevant effect on the PK of tixagevimab and cilgavimab.

5.3 Preclinical safety data

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

Non-clinical data reveal no special hazard 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Sucrose
Polysorbate 80 (E 433)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years

Prepared syringes

The prepared syringes should be administered immediately. If immediate administration is not possible, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 4 hours at 2ºC to 25ºC.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Store in the original package in order to protect from light.
Do not freeze.
Do not shake.

For storage conditions after initial vial puncture and preparation of the syringes, see section 6.3.

6.5 Nature and contents of container

Tixagevimab vial

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

Cilgavimab vial

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

Pack size: Each carton contains 2 vials: 1 vial of tixagevimab and 1 vial of cilgavimab.

6.6 Special precautions for disposal and handling

Handling instructions

This medicinal product should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.

Inspect the vials visually 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.

Each dose of tixagevimab and cilgavimab is withdrawn into two separate syringes, to be administered intramuscularly in two different muscles, preferably in the gluteal muscles.

For storage conditions of the prepared syringes, see section 6.3.

Any unused solution should be discarded.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1651/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 March 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

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

Lonza Biologics
101 International Drive,
Portsmouth, NH 03801,
USA

WuXi Biologics Co., Ltd.
108 Meiliang Road,
Mashan, Binhu District, Wuxi, Jiangsu 214092,
People's Republic of China

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtunavägen,
SE-152 57 Södertälje,
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

EVUSHELD 150 mg + 150 mg solution for injection
tixagevimab + cilgavimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of tixagevimab contains 150 mg of tixagevimab in 1.5 mL (100 mg/mL).
Each vial of cilgavimab contains 150 mg of cilgavimab in 1.5 mL (100 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80 (E 433), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial tixagevimab
1 vial cilgavimab
tixagevimab 150 mg/1.5 mL
cilgavimab 150 mg/1.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original package in order to protect from light.
Do not freeze.
Do not shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1651/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

EVUSHELD 150 mg injection
tixagevimab

IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg/1.5 mL

6. OTHER

AstraZeneca

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

EVUSHELD 150 mg injection
cilgavimab

IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg/1.5 mL

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the user

EVUSHELD 150 mg + 150 mg solution for injection
tixagevimab + cilgavimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before the medicine is given because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EVUSHELD is and what it is used for

EVUSHELD is made up of two active substances: tixagevimab and cilgavimab. These are both medicines called *monoclonal antibodies*. These antibodies are proteins that attach to a specific protein of SARS-CoV-2, the virus that causes COVID-19. By attaching to this protein, they prevent the virus from entering human cells.

EVUSHELD is used for the pre-exposure prophylaxis (prevention) of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

EVUSHELD is used to treat adults and adolescents, aged from 12 years and weighing at least 40 kg, with COVID-19 who:
- do not require supplemental oxygen to treat COVID-19, and
- are at increased risk for the illness becoming severe based on the evaluation of your doctor.

2. What you need to know before you are given EVUSHELD

You must not be given this medicine
- if you **are allergic** to tixagevimab, cilgavimab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given EVUSHELD
- if you have low numbers of blood platelets (which help blood clotting), any blood clotting problems or are taking a medicine to prevent blood clots (an anticoagulant).
- if you have ever had a severe allergic reaction or breathing problems after you were given EVUSHELD in the past.

COVID-19 is caused by different variants of the SARS-CoV-2 virus that change over time. EVUSHELD may be less effective at preventing COVID-19 caused by some variants than others. Contact your doctor right away if you get symptoms of COVID-19. COVID-19 affects different people in different ways:

- 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.

Tell a doctor, pharmacist or nurse or get medical help immediately:

- if you notice any symptoms of a **cardiac event**, such as:
  - chest pain;
  - shortness of breath;
  - a general feeling of discomfort, illness, or lack of well-being;
  - feeling lightheaded or faint.
- if you notice any signs of a **severe allergic reaction**, such as:
  - difficulty breathing or swallowing;
  - swelling of the face, lips, tongue or throat;
  - severe itching of the skin, with a red rash or raised bumps.

Children and adolescents
EVUSHELD should not be given to children under 12 years of age or weighing less than 40 kg.

Other medicines and EVUSHELD
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because it is not yet known if this medicine affects other medicines, or if it is affected by them.

Pregnancy and breastfeeding
Tell your doctor or nurse if you are pregnant, or if you might be pregnant.

- This is because there is not enough information to be sure that this medicine is safe for use in pregnancy.
- This medicine will only be given if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child.

Tell your doctor or nurse if you are breast-feeding.

- This is because it is not yet known whether this medicine passes into human breast milk, or what the effects might be on the baby or milk production.
- Your doctor will help you decide whether to keep breast-feeding or to start treatment with this medicine.

Driving and using machines
It is unlikely that EVUSHELD will affect your ability to drive or use machines.

EVUSHELD contains polysorbate 80
This medicinal product contains 0.6 mg of polysorbate 80 in each vial of tixagevimab and in each vial of cilgavimab. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How EVUSHELD is given

The recommended dose for pre-exposure prophylaxis (prevention) is 300 milligrams (mg), given as two injections:

- 150 mg of tixagevimab
- 150 mg of cilgavimab

The recommended dose for treatment of mild to moderate COVID-19 is 600 milligrams (mg), given as two injections:
- 300 mg of tixagevimab
- 300 mg of cilgavimab

EVUSHELD consists of two separate solutions, one containing tixagevimab and one containing cilgavimab. They will be given to you by your doctor or nurse who will **inject each one into a separate muscle,** usually one into the muscle of each buttock. The 2 injections will be given one after the other.

Your doctor or nurse will decide how long you will be monitored after you are given the medicine. This is in case you have any side effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects
Common (may affect up to 1 in 10 people)
- hypersensitivity reaction (rash or an itchy red rash or raised bumps)
- injection site reaction (pain, redness, itching, swelling near where the injection was given)

Uncommon (may affect up to 1 in 100 people)
- injection related reaction (examples of these include headache, chills and redness, discomfort or soreness near where the injection was given)

Rare (may affect up to 1 in 1000 people)
- sudden, severe allergic reaction with breathing difficulty, swelling, light headedness, fast heartbeat, sweating and loss of consciousness (anaphylaxis)

Reporting of side effects
If you get any side effects, **talk to your doctor, pharmacist or nurse**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EVUSHELD

Keep this medicine out of the sight and reach of children.

Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Unopened vials:
- Store in a refrigerator (2°C-8°C).
- Do not freeze.
- Do not shake.
- Store in the original package in order to protect from light.

Prepared syringes should be used immediately. If necessary, store the prepared syringes for no more than 4 hours at 2°C to 25°C.

6. Contents of the pack and other information

What EVUSHELD contains

The active substances are:

- tixagevimab – 150 mg in 1.5 mL of solution.
- cilgavimab – 150 mg in 1.5 mL of solution.

The other ingredients are histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80 (E 433) and water for injections.

What EVUSHELD looks like and contents of the pack

EVUSHELD contains two clear glass vials of solution for injection:

- Tixagevimab solution for injection (dark grey cap) is a clear to opalescent, colourless to slightly yellow solution.
- Cilgavimab solution for injection (white cap) is a clear to opalescent, colourless to slightly yellow solution.

Each carton contains 2 vials: 1 vial of tixagevimab and 1 vial of cilgavimab.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Administration

- This medicinal product should be handled by a healthcare professional using aseptic technique to ensure the sterility of each dose.
- Tixagevimab and cilgavimab should be inspected visually for particulate matter and discolouration prior to administration. 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.
- After initial puncture vials, if not used immediately, the medicinal product in the vial can be stored for 4 hours at 2°C to 25°C. In-use storage times and conditions are the responsibility of the user.
- Withdraw the required dose of tixagevimab in one syringe and withdraw the required dose of cilgavimab in a separate syringe. The two separate syringes to be administered intramuscularly in two different muscles, preferably in the gluteal muscles.
- An additional overfill is included in each vial to allow the withdrawal of 1.5 mL. Discard any unused portion left in the vial.
- The prepared syringes should be administered immediately.
- If immediate administration is not possible, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 4 hours at 2ºC to 25ºC.

Any unused solution or waste material should be disposed of in accordance with local requirements.